As a growing wave of designer drugs hits the streets, researchers try to forecast which will prove most popular—and dangerous

By Emily Underwood

Roughly 2 years ago, just before her 24th birthday, Tessa Shlaer went with a friend to the back aisles of an adult superstore in Gwinnett County, Georgia, and bought three clear jars, each containing an ounce of a cloudy white substance. The jars bore different brand names—“Meow Meow,” “Bolivian MDPV,” and “Miami Ice”—and the contents of one resembled crumbling lumps of sugar; another, shards of glass; the third, white powder. Later, at a hotel room a few hours’ drive away, Shlaer and her friend lit the white crystals from one jar in a methamphetamine pipe. The smoke, she recalls, had a sickly odor that lodged in her nose—a combination of scorched rubber and vanilla hand soap. “There was a sweetness, a chemical smell, like something that’s not supposed to be burned.”

Shadowy figures soon appeared in her peripheral vision and urged her to do violent and self-destructive things. As the hours, then days, marched on in that hotel room, Shlaer and her friend binge-smoked, injected, and snorted nearly all the contents of the jars. She fantasized about tearing human flesh with her teeth and scraped her face and body with her nails in violent fits.

Shlaer is a recovering cocaine addict and had used methamphetamine before, but she always thought she could tell the difference between her own mind and her mind on drugs. In that hotel room, she couldn’t. “For the first time, I felt evil,” says Shlaer, who was studying to become a paramedic when drug use derailed her academic plans.

The jars Shlaer bought most likely contained a mix of powerful stimulants called synthetic cathinones. Often referred to as “bath salts,” “research chemicals,” or “plant food,” these compounds belong to a rapidly expanding array of substances that mimic or increase the effects of an illegal drug. Yet they mostly slip past law enforcement, their formulas tweaked just enough to skirt existing regulations or to go undetected in a drug test.

Evaluating the addictiveness of those drugs, deciphering how they work in the brain, and predicting which are likely to become a major threat is the job of a small lab at the National Institute on Drug Abuse (NIDA) in Baltimore, Maryland, headed by neuroscientist Michael Baumann. Set up in 2012, the four-person lab only takes on drugs that have at least 1000 mentions in the National Forensic Laboratory Information System, a U.S. drug surveillance program run by the Drug Enforcement Administration (DEA). Still, the team sometimes screens as...
Baumann is part of a small but growing fraternity of researchers worldwide fighting back against science that has broken bad. Designer drug labs, Baumann notes, operate much like pharmaceutical companies, mining the existing scientific literature to find a new blockbuster. Rather than hunting for therapies, however, chemists in designer drug labs often seek out compounds that were abandoned because they were too dangerous or habit-forming, he explains. “They’re looking for the things that will be most addictive.” Baumann’s task is to sound the alarm when he believes they have succeeded.

**MOST DESIGNER DRUGS** are not produced in a mobile home trailer like the one where methamphetamine is brewed in the TV series *Breaking Bad*, notes Jim Hall of Nova Southeastern University, Fort Lauderdale, in Florida, who studies the epidemiology of drug outbreaks. Instead, Hall says, they come from large-scale manufacturers in China, India, and Pakistan, often operating out of former chemical or perfume plants. Dealers order many of the compounds, including synthetic cathinones, in bulk, then put the raw product into empty pill capsules or sell it in baggies or jars, giving it a popular or local brand name.

Historically, Europe has led the world in designer drug consumption and surveillance. According to the European Monitoring Centre for Drugs and Drug Addiction, 73 previously unknown psychoactive substances hit European markets in 2012 alone. In the United Kingdom, the problem is so extreme that researchers have started diving for data in latrines: Just last year, they discovered 13 unknown new psychoactive drugs over the course of 6 months by sampling urine from central London’s portable toilets.

In recent years, however, the number of new designer drugs appearing first in the United States—rather than migrating from Europe—has skyrocketed, says Jill Head, a supervisory chemist at DEA. Since 2009, Head and her colleagues, whose job is to analyze seized compounds and determine their chemical structure, have identified more than 300 new drugs, she says. In response to the crisis, NIDA last year launched a 5-year project called the National Drug Early Warning System, or NDEWS, which aims to create a network of scientists, public health experts, and law enforcement representatives for sharing information and assisting with local drug research.

The largest percentage of new chemicals found in U.S. drug busts are synthetic cannabinoids—drugs marketed as marijuana imitators that don’t show up in standard drug tests (see sidebar, p. 473). Synthetic cathinones come in second; as of late 2010, Head and her colleagues had found 70 new, synthetic permutations of the cathinone molecule, which is made by the khat plant *Catha edulis*. People have chewed khat for its mild stimulant qualities for hundreds of years, and safe, modern-day versions of the compound can be found in drugs as widely prescribed as the antidepressant Wellbutrin.

But tinker with the molecule’s structure in key places—a methyl group here, a few oxygens there—and you can produce many psychoactive compounds, including powerful stimulants and hallucinogens (see chart, p. 472). “The sheer number of possibilities can be staggering,” Head says.

Shlaer’s first experience with bath salts came a few weeks before her visit to the Georgia superstore—and it was inadvertent. She injected methamphetamine that hospital blood tests later showed had been cut with two synthetic cathinones, methylone and MDPV. The consequences were dramatic: intense euphoria, heightened interest in everything, and the desire to be in constant motion, followed by nightmarish visions and suicidal despair. As soon as the drugs began to wear off, however, Shlaer became consumed with the desire to try them again.

“I could not stop thinking about and researching bath salts.”

Tessa Shlaer, recovering addict

Shlaer had experienced two of the first synthetic cathinones to hit the United States. By the time she tried them, they were already illegal. Starting around late 2010, alarming reports of fatal overdoses, as well as a rash of grisly shootings and other violent crimes linked to the drugs, were pouring in from around the country. In 2011, DEA placed a 2-year emergency ban on methylone, MDPV, and a third substance called mephedrone, and began working with the agencies of the Department of Health and Human Services to determine whether the ban should be permanent.

Once a drug has been banned, obtaining samples for study becomes difficult for many scientists. They must possess or apply for a special DEA license in order to work with even minuscule amounts. But NIDA
holds an institutional license to work on illegal drugs, and it has an annual budget devoted to studying designer drugs, which in-house chemists can synthesize to order. As a result, Baumann and colleagues are uniquely equipped to act quickly when a new drug hits the street.

After getting samples of the cathinones—in this case, from a colleague at the University of Wisconsin—Baumann sent them to John Partilla, a research chemist with an appropriate nickname: the Gatekeeper. One of Partilla’s roles is to determine which drugs have the potential to be addictive or otherwise dangerous and which the lab can safely ignore.

In the case of the psychostimulants found in bath salts, the answer to that question lies in how they interact with key pieces of neuronal machinery called monoamine transporter proteins. When a neuron fires a signal to its neighbors, it releases a burst of neurotransmitter molecules into the gap between the cells, called the synapse. The neurotransmitters bind to receptors on adjacent neurons, transmitting the chemical signal, but then quickly drop off. The first cell, which sent the signal, uses the transporter proteins to vacuum up the neurotransmitter, removing it from the synapse. If that does not happen, the lingering neurotransmitter molecules will continue to bind with receptors on the neighboring cells, sending and resending an aberrant, repetitive message.

Psychostimulants act on the transporter for the neurotransmitter dopamine, a key pleasure molecule in the brain, boosting its levels in the synapse. Methamphetamine, for example, slips through the transporter to trick the cell into releasing more dopamine, “essentially throwing the vacuum cleaner into reverse,” Baumann says. Cocaine acts more like a rolled up sock in a vacuum hose, he explains. It blocks the transporter from vacuuming dopamine out of the synapse. In either case, as excess dopamine builds up in the synapse, it stimulates neuronal activity in regions that are involved with feelings of pleasure and its anticipation, generating an intense high that addicts come to crave.

To determine how MDPV, methylone, and mephedrone affect the dopamine transporter, Partilla delicately ground up rat brain tissue with a mortar and pestle, then put the tissue into a test tube and spun it in a centrifuge to separate its component parts. He collected assemblies of membranes and proteins, called synaptosomes, which include the transporters. When in solution, the cell membranes and their proteins will obligingly reassemble themselves into round, miniature nerve endings, Baumann
Designed to be addictive

A small sample of synthetic cathinones seized by DEA in recent years; as of 2010, the agency had found 70 new variations on the cathinone molecule (center).

Not directly advise DEA, but the agency often uses such information to decide how to “schedule” a new drug according to a five-level ranking system, with Schedule I drugs considered the most addictive and dangerous, says DEA spokeswoman Barbara Carreno. In 2012, DEA permanently listed all three synthetic cathinones as Schedule I substances.

WHY MDPV’S CHEMICAL STRUCTURE is so much more potent at blocking the dopamine transporter than cocaine or any other cathinone-based molecule remained unclear. The question is not merely academic, says Louis De Felice, a biophysicist at Virginia Commonwealth University in Richmond. If scientists can determine precisely how a drug binds to its target in the brain, they can sometimes devise an antidote that dislodges the compound or counteracts it. The drug naloxone, for example, binds to the same neuronal receptors as heroin and can stop and even reverse an overdose by blocking heroin’s effects. In the United States, naloxone has been responsible for reversing the effects of a heroin or other opioid overdose in more than 10,000 people since 1996, according to a 2010 survey by the Centers for Disease Control and Prevention.

In hopes of finding a similar antidote for MDPV and related designer drugs, Baumann, De Felice, and a handful of other researchers have begun to deconstruct the molecule piece by piece, as well as the dopamine transporter protein to which it binds. In December 2012, De Felice and one of his Ph.D. students, Krasnodara Cameron, made a bet over which parts of MDPV’s chemical structure made it so potent. Was it the three-carbon propyl hook attached to the body of the molecule like a zigzagging arm? Or was it the molecule’s pentagonal head, called a pyrrolidine ring?

Cameron bet on the head, De Felice on the hook. The stakes were high: a batch of homemade cookies, winner’s choice. “Sweets,” De Felice calls sugary treats. After all, he says, “we’re all driven by dopamine.”

Renata Kolano, a synthetic chemist in De Felice’s lab at the time, systematically created MDPV derivatives missing different parts of the molecule, which the team tested in experiments similar to those used in Baumann’s lab to screen new drugs. The ring and the hook both turned out to be vital to MDPV’s ability to jam the dopamine transporter, like cocaine. It did—and the synthetic compound turned out to be 10 times more potent than cocaine at blocking dopamine uptake. When other members in Baumann’s lab injected rats with the drug, it produced large, long-lasting dopamine spikes in their brains, comparable to those triggered by much higher doses of cocaine.

The rats’ behavior on the drug was also extreme, Baumann says: They jumped and reared and often bobbed their heads and sniffed uncontrollably—an animal model of psychosis in humans. They avidly self-administered injections of the drug by pressing a lever. Taken together, Baumann recalls, the evidence added up to “red alert”—indicating MDPV’s risk for abuse and addictiveness. Baumann’s lab says: “They basically form with the proteins all oriented in the proper direction.”

Next, Partilla loaded the synaptosomes with radioactive dopamine, allowing him to precisely trace how much of the neurotransmitter escaped the miniature nerve endings when they were exposed to one of his drug samples. Both methylene and mephedrone slipped through the dopamine transporters into the droplets and immediately triggered a burst of neurotransmitter release, which mimics the mechanism of methamphetamine and means they are likely addictive.

The MDPV story was more complicated. It didn’t slip through the transporter. So Partilla performed a second experiment to see whether MDPV instead jammed the dopamine transporter, like cocaine. It did—and the synthetic compound turned out to be 10 times more potent than cocaine at blocking dopamine uptake. When other members in Baumann’s lab injected rats with the drug, it produced large, long-lasting dopamine spikes in their brains, comparable to those triggered by much higher doses of cocaine.

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Alarm over synthetic cannabinoids

By Emily Underwood

Crimes media reports of cannibalism and shooting sprees prompted by synthetic cathinones (see main story, p. 469) have given them an especially bad reputation, but there’s another class of designer drugs worrying drug enforcement and public health officials: synthetic cannabinoids, humanmade chemicals designed to mimic THC, the key psychoactive ingredient in marijuana.

The drugs are typically sprayed onto dried plant material so they can be smoked. They are billed as providing marijuana-like highs while eluding drug tests. Sold since the early 2000s under brand names such as K2 and Spice, they act on the same brain receptors as THC but are up to 100 times more potent, leading to dangerous side effects such as heart attack, kidney failure, psychosis, and sometimes death. Many people underestimate the risk of synthetic cannabinoids because they see marijuana as benign, says Marilyn Huestis, a toxicologist at the U.S. National Institute on Drug Abuse (NIDA) who is developing tests for the drugs in blood, saliva, urine, and breath. “People are less afraid of a joint than they are of a white powder.”

Since the Drug Enforcement Administration banned the first synthetic cannabinoids in 2011, more than 250 new compounds have arisen to take their place. In a recent study of 20,017 samples of urine collected from U.S. military service members worldwide between July 2011 and June 2012, Huestis and her colleagues found traces of the compounds in 290 of them. And according to a 2012 NIDA-funded survey, one in nine 12th graders in the United States reported using synthetic cannabinoids in the past year.

transporter, De Felice says. (Cameron still made him peanut butter cookies.)

Baumann, De Felice, and their colleagues then went a step further, dismantling the alkyl chain that forms the hook piece by piece and testing the resulting molecules in rodents. The shorter it got, the less potent the drug became. Such painstaking work “provides a high level of predictive power” for researchers examining a new designer drug, Baumann says. “We can now look at a drug on a cathinone scaffold and say we know how this drug will affect transporter function and influence behavior.”

In the meantime, a new crop of potent synthetic cathinones is already wreaking havoc in U.S. communities. Although reports of MDPV dropped precipitously after it was banned in 2011, designer drug-makers were far ahead of the curve. At almost the same time, DEA surveillance reports of a drug called α-PVP, widely known as “gravel” in the Northeast, shot up from a total of roughly 20 to more than 3000. When α-PVP first hit the streets, Baumann suspected it would have psychological and physical effects similar to those of MDPV, based on the compounds’ structural similarity. In 2013, he ordered samples of the compound and ran it through the same tests he had applied to MDPV. He found that it did act almost exactly like the banned drug—a finding that supported DEA’s decision to outlaw α-PVP in 2014.

WEEKS AFTER

her hotel room binge, Shlaer says her paranoid hallucinations remained so vivid that she called the police,

Shlaer experiences hallucinations, occasional cravings for bath salts, and sudden bouts of rage, she says. Last winter, desperate for more information, she remembered a name she had read while researching the drugs: Louis De Felice.

“I am not really sure how appropriate it is for me to be emailing you,” Shlaer wrote him. Apologizing for her scattered state, she added, “no one here has ever dealt with bath salts’ long term effects before. Do you know of anyone I could talk to or with whom I could correspond?”

Although De Felice gets many such letters from addicts, Shlaer’s message, which described her experiences in articulate detail, stood out, he says. He wrote back immediately: “You don’t sound scattered, you sound rational, sincere and in trouble.”

De Felice told Shlaer that evil intentions, hallucinations, and rage are all common symptoms of bath salts overdose. And he invited Shlaer to come to his university to see the lab and talk to some of his students about her experiences. The trip last spring was “incredible,” Shlaer notes. The undergraduates she spoke to “were actually interested in what I had to say, from a human and a scientific perspective.” She is now considering a career in biomedical research, which De Felice says he will help her pursue. And she is resuming her training to become a paramedic. Although drugs are never far from her mind, she says, “now, my thoughts are of a more clinical nature.”

Research chemist John Partilla screens emerging designer drugs at the National Institute on Drug Abuse, looking for those likely to be most addictive.