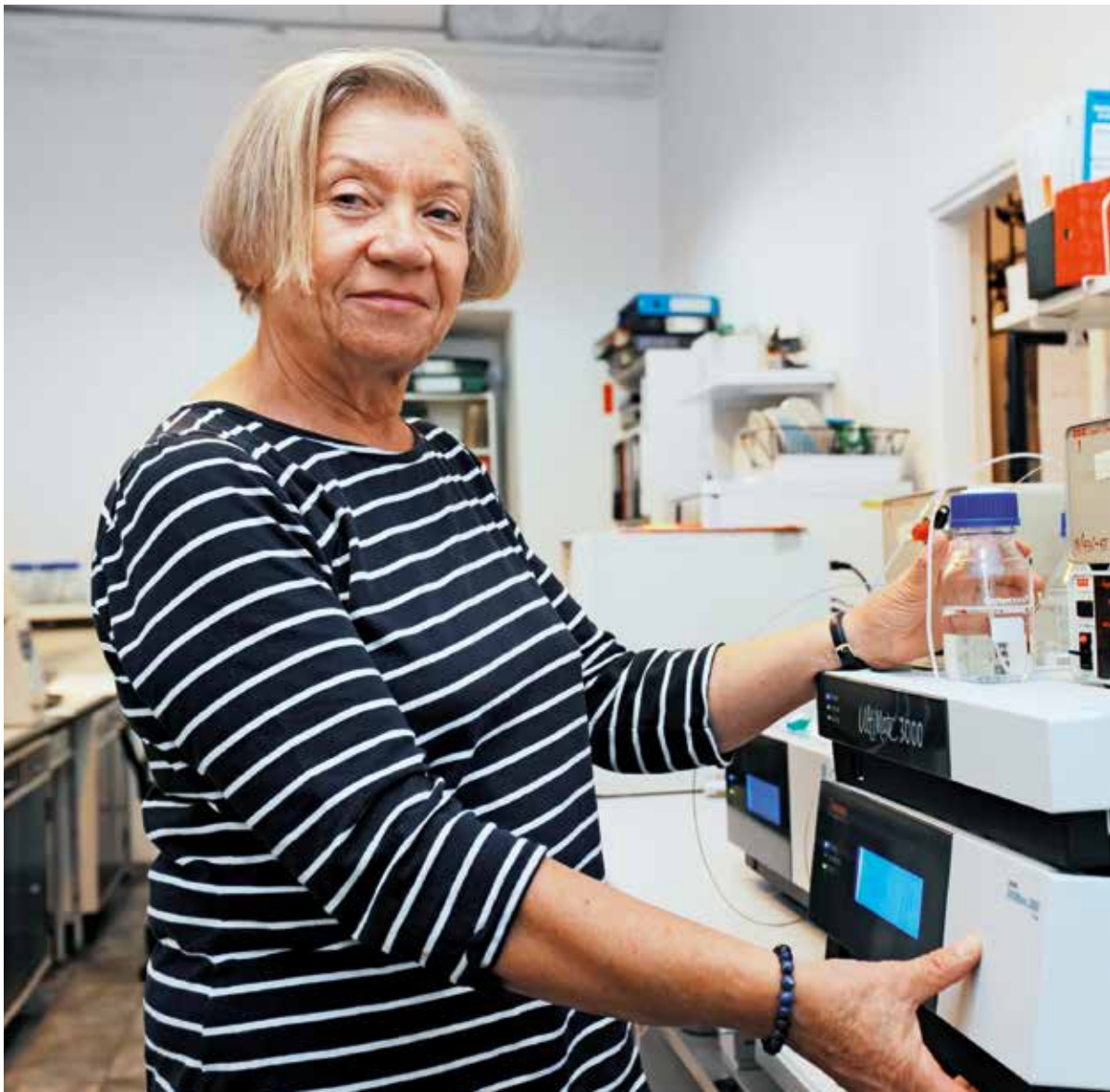
ACADEMIA Pharmacology

The Dark Side of Designer Drugs

Designer drugs cause irreversible changes in the brain and put those who take them at an increased risk of developing Alzheimer's and Parkinson's disease. They can also affect one's genetic material, says **Prof. Krystyna Gołembiowska** from the PAS Institute of Pharmacology.

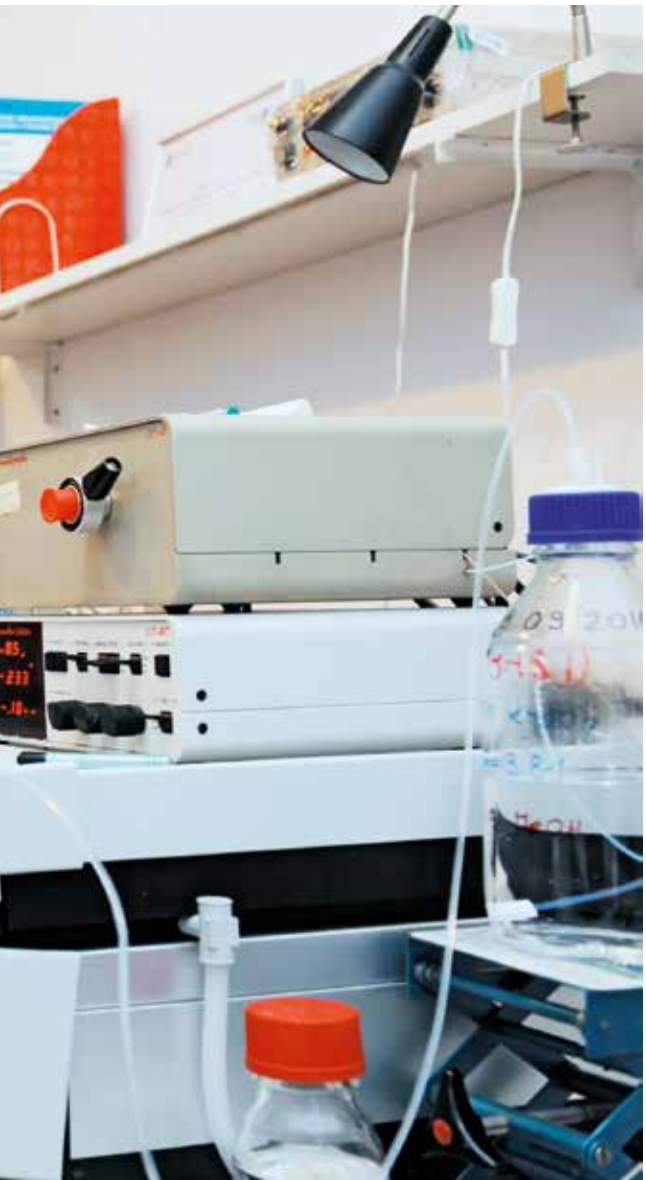


JAKUB OSTAŁOWSKI

ACADEMIA: **In recent years, the media have been quite active in covering issues related to a wide range of psychoactive substances known as "designer drugs" or "legal highs." Every now and then, the authorities declare a war on the dealers, but always end up losing. Most of us have heard about these substances, but our knowledge is limited to the belief that they are probably harmful. What else should we know about designer drugs?**

KRYSTYNA GOŁEMBIOWSKA: Designer drugs, just like other psychoactive substances, are available on the market because humans want to feel better, enhance their physical and mental performance, increase sensations, or feel more at ease in interpersonal relations. Humans have used such substances practically since the beginning of their history. In many cultures, shamans made plant mixtures that caused alterations in consciousness. Studies of those mixtures led to the discovery of such substances as psilocybin, produced by mushrooms, and THC, found in marijuana.

Many modern psychoactive substances were developed during the search for new drugs, especially antidepressants. One good example is MDMA, or 3,4-methylenedioxymethamphetamine, a principal component of ecstasy that was first synthesized by Alexander Shulgin. Initially, Shulgin did not even realize the psychedelic properties of MDMA. He found out later from one of his students.



Its history is similar to that of LSD.

Yes. All these events occurred in the late 1960s and early 1970s in the United States, where psychoactive substances gained popularity – not only LSD but also amphetamine. Their producers began observing the work of pharmacologists and chemists and attempted to create new chemical compounds. Substances used to model various psychiatric disorders served as a basis for the production of many compounds known as designer drugs.

What are test substances?

In pharmacology, these are the substances that are administered to test animals to induce a certain condition, such as depression or psychosis, and to check if newly-designed drugs can alleviate it. Unfortunately, designer drug manufacturers take advantage of the acquired knowledge about numerous test substances, some altering the functions of the nervous system.

In the previous issue of *Academia* magazine, we talked to the pharmacologist Prof. Stanisław Czuczwar, who pointed out that the biggest problem with designer drugs was their vast diversity: patients who end up in hospital emergency rooms after taking such substances can only be treated for symptoms, because the doctors don't know exactly what substances they took.

Yes, there are so many psychoactive substances on the market that lawmakers can't keep pace with imposing relevant restrictions. In order for a substance to be included on the list of controlled substances, it must be tested very thoroughly. It is also necessary to describe its mechanism of action at the physiological level, determine the toxic effect it has on specific organs, and so on. Science stands no chance against designer drug manufacturers, as more and more substances continue to hit the market. We can only draw conclusions about their mechanism of action by observing people under the influence of such substances, but that is not enough to say exactly which structures of the brain and metabolic pathways are affected.

The kind of research we do is not just about getting certain substances onto the list of controlled substances. MDMA is currently a test substance used in studying neurodegenerative processes in the brain. Our society is aging and diseases linked to neuronal damage such as Alzheimer's or Parkinson's diseases are increasingly common.

Prof. Krystyna Gołembiowska
is head of Team II at the Pharmacology Department, PAS Institute of Pharmacology, studying the effects of new psychoactive substances (NPS) on the human body. Since 2014, she has been carrying out the three-year project "Designer Drugs: Effects on the Central Nervous System and Neurotoxicity" under a grant from Poland's National Science Center (NCN).

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One and the same symptom can be caused by different mechanisms.

Of course. That's why animal tests are conducted and neurochemical changes in the brain are analyzed. Our team studies derivatives of amphetamine such as MDMA. It is a very popular substance, both a stimulant and an antidepressant. It is described as an empathogen, because it makes it easier to establish interpersonal contacts.

Does its mechanism of action differ from that of amphetamine?

Yes. At the same time, it is very dangerous. Amphetamine affects dopaminergic neurons by causing an increased release of dopamine, which is a natural neurotransmitter present in the brain. Also, it indirectly affects other structures reached by neural pathways that run from the dopaminergic structures. Compounds similar to amphetamine mimic the effects of dopamine. But they also cause a much higher than normal release of dopamine and the effects resemble an avalanche, because consecutive structures in the brain are stimulated. MDMA also stimulates serotonergic neurons, thus further broadening this avalanche-like reaction. MDMA, which is found in ecstasy pills, is on the list of controlled substances and is therefore difficult to obtain. That's why designer drug producers also add in other substances to ecstasy pills.

> Young people are usually unaware of the negative effects of designer drugs. Education is important, because legal bans typically prove counterproductive.

How do they obtain such substances?

I think that the chemists who work for criminals develop new substances simply by trial and error. They try to alter functional groups in molecules and change their chemical structure in various ways. No one tests the substances obtained in this way; those who use them are acting as guinea pigs. We can get to know the actual mechanism of action of such substances only after putting a great deal of effort into identifying them. That's the task of forensic toxicology. Based on information from this branch of science, scientists try to determine the properties of new compounds and their mechanism of action.

If the components of designer drugs were not so harmful to society, scientists would have ceased to take an interest in them a long time ago. Once the mechanism of action of the psychoactive substances popular in the 1970s such as MDMA and LSD was described in detail, the testing stopped, because there was not much left to discover. It was not until the Internet emerged and facilitated trade in designer drugs that new substances seized by the police started to reach pharmacological laboratories.

It is difficult to understand why the users of designer drugs accept the high risk involved in taking such substances.

In the past, young people would buy a candy bar and cola on their way to school. When "smart shops" appeared, they started to buy psychoactive substances. For that reason, it's good that the sale of designer drugs has been delegalized. Although the business largely moved to the Internet, young people have more difficulty obtaining such substances, because they need to have a bank account or a credit card and provide a mailing address, so it is easier for their parents to control such behavior.

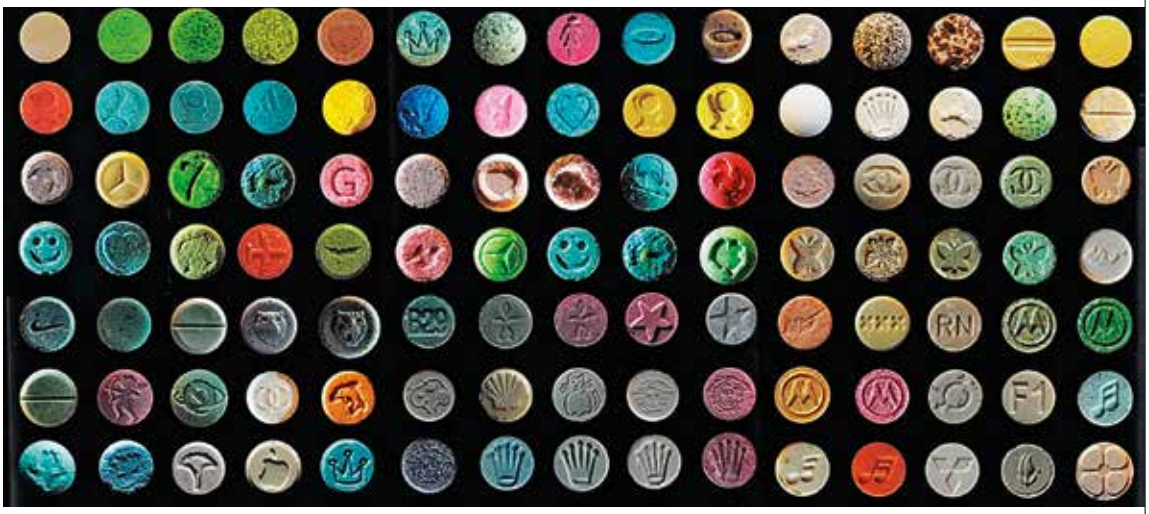
Do psychoactive substances have different effects on young people than on adults?

Many psychoactive substances have different effects on a brain that is still maturing than one that is already mature. In a maturing brain, certain mechanisms are not yet fully developed or are still changing. If a maturing brain is subjected to neurotoxins, the resulting changes will be irreversible. Studies we have conducted using animal models confirm this. We have discovered that if some of the substances found in designer drugs are administered to adolescent rats, this not only changes their behavior but also causes long-term damage to genetic material observed in the adult period. Very few people realize that it is impossible to reverse neurodegenerative changes once they have occurred. Adolescents who take psychoactive substances may be also more likely to develop addictions to such substances, even after taking small doses.

Can the damage to genetic material be passed on to the offspring?

We don't know for sure, but the changes that psychoactive substances cause in parents may make their children more prone to certain diseases. No such studies have been conducted with respect to ecstasy, but we know that such a common substance as caffeine, when consumed excessively during pregnancy, alters the sensitivity of adenosine receptors. Adenosine is an endogenous substance that modulates the action of other classical neurotransmitters in the brain such as dopamine. That is a cascade reaction in which a change in the sensitivity of one receptor leads to changes in the entire brain.

It's necessary to stress that, unlike designer drugs, caffeine is generally believed to have beneficial effects,



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MDMA, once the principal component of ecstasy, is now being mixed by designer drug manufactures with numerous other substances. Unfortunately, the pills are colored and stamped with different logos, so they look like harmless candies.

because it blocks the depressive effects of adenosine. In other words, it makes you less sleepy and more active, you can think better. That's the reason why pure caffeine started to be included in ecstasy pills; the blocking of the inhibitory system in the brain caused by caffeine was coupled with the effects of MDMA. Studies on animals show that such a mixture of psychoactive substances is very dangerous for the brain.

After such a massive release of neurotransmitters, does it take more time to return to the normal state?

A strong stimulation of neurons leads to the rapid release of neurotransmitters. At some point, they may run short, because cells can't synthesize them fast enough. The stimulation caused by designer drugs is therefore followed by a shortage of dopamine or serotonin, which negatively affects mood and impairs the functioning of the human body.

In addition, a massive release of neurotransmitters as a result of stimulation caused by designer drugs leads to oxidative stress, causing the production of free radicals, which damage DNA and other components of the cell. In the long term, such damage may lead to neurodegenerative diseases such as dementia, depression, Alzheimer's or Parkinson's disease.

Are there any clinical studies in this field that involve human beings?

Clinical research chiefly relies on hospital case studies, whereas basic research relies on the results of studies involving animals. In our team, for example, we studied mephedrone, a synthetic derivative of cathinone, an alkaloid found in nature in the plant called khat (*Catha edulis*). Mephedrone is similar to amphetamine in terms of its mechanism of action. After mephedrone was delegalized, chemical analogs of this substance appeared on the market of designer drugs. In essence, the only difference was the location of substituents in the molecule. Synthetic cathinones are extremely toxic. We have conducted studies on animal models that show that even a single dose of such compounds causes the degradation of the neuronal DNA.

Does the risk of poisoning depend only on the type of substance or also on the dose?

Paracelsus, the father of toxicology and modern medicine, said that "poison is in everything, and no thing is without poison" – it is the dose that makes the poison. Even pure water, if consumed in excessive amounts, may prove to be a poison. Unfortunately, those who take designer drugs never know what they take exactly and in what doses. Abuse of some substances, for example LSD, causes tolerance: colloquially speaking, the body needs a greater dose to get the same results. Currently available substances that mimic the effects of LSD are effective in very small doses, so they can be easily overdosed and cause death.

However, those who take such substances probably think that taking more will bring better results. Is there any way to prevent such poisonings?

Prof. Jolanta Zawilska from the Medical University of Łódź popularizes knowledge of designer drugs. She has also published a brochure on designer drugs addressed to schoolchildren. Young people know the so-called positive results of designer drugs, but they are usually unaware of the negative effects. The only thing we can do is educate society, because legal bans usually prove counterproductive. Of course, legal measures can be used to restrict or hinder access to designer drugs, but this will not stop people who are determined to take them. It is therefore worth making young people realize how much harm they could do to their bodies.

INTERVIEW BY **AGNIESZKA KLOCH**