The Pharmacologist

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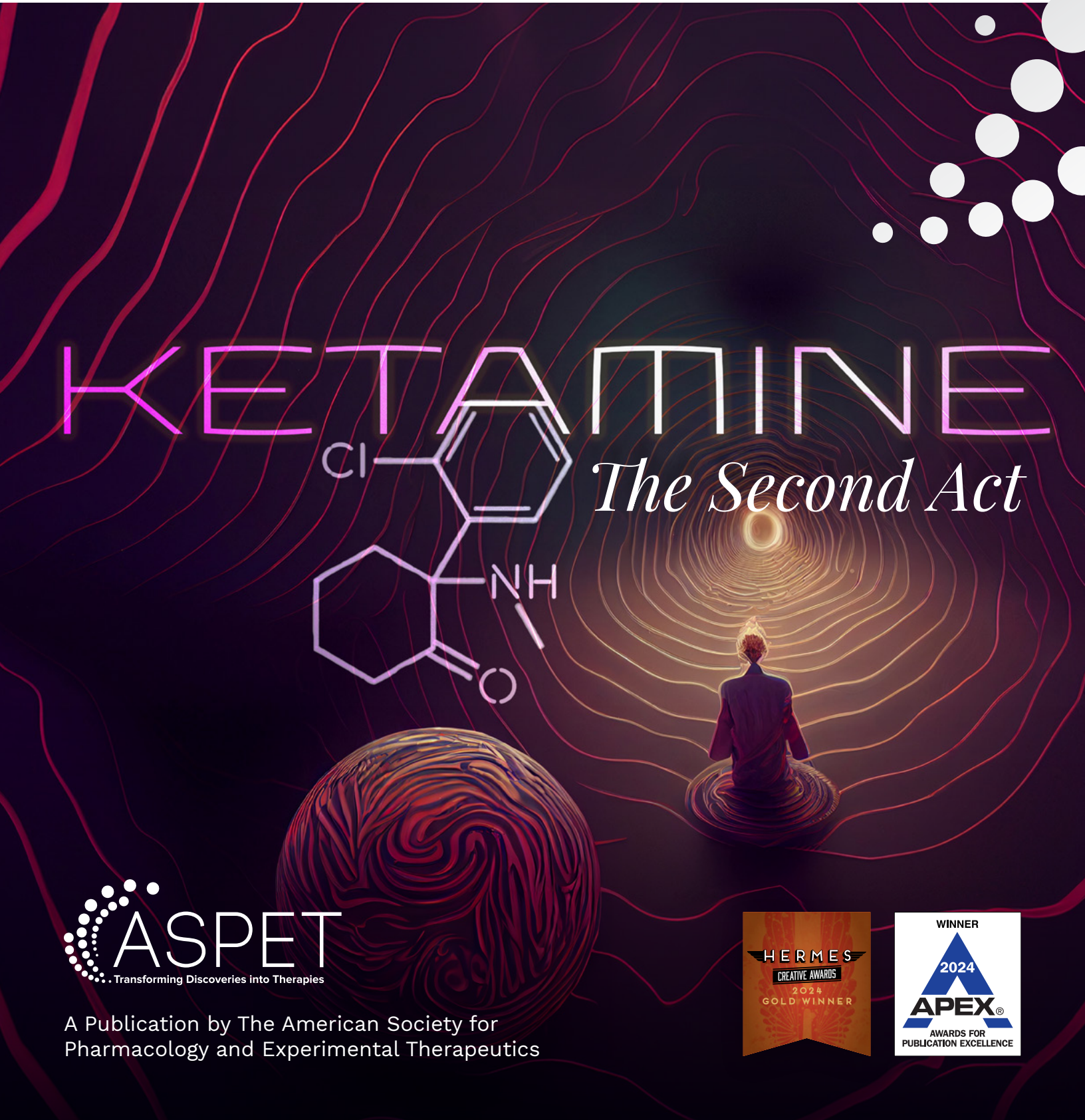

ASPET
Transforming Discoveries into Therapies

A Publication by The American Society for Pharmacology and Experimental Therapeutics

In this Issue

On the Cover: *Dissociative ketamine. Chemical formula, molecular structure.*

The Pharmacologist is published monthly by the American Society for Pharmacology and Experimental Therapeutics, 1801 Rockville Pike, Suite 210, Rockville, MD 20852.

Message from the President

Listen to ASPET President, Dr. Carol Beck, give updates on ASPET 2025 abstract submissions, our expanded list of countries eligible for reduced membership rates and more!

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A Note from Dave's Desk

September: A Month to Celebrate Our Community

September is a unique month that celebrates two overlapping, though certainly important, parts of the ASPET community: National Postdoc Appreciation Week (NPAW) and Peer Review Week.

NPAW was formally started in 2009 by the National Postdoctoral Association (of whom ASPET is an Associate member) to recognize the significant contributions that postdoctoral scholars make to U.S. research and discovery. This year, NPAW will take place September 16–20, 2024, with a wide variety of events being held by the entire biomedical community to create awareness and appreciation of the role postdocs play in scientific research. ASPET is proud to call hundreds of postdocs members of the Society as we aim to provide the resources and support their community needs. For example, ASPET provides postdocs with travel awards to the attend the ASPET Annual Meeting, opportunities to gain new professional development skills through the ASPET Mentoring Programs, including our new ASPET MentorMatch, and recognition for excellent articles published in one of ASPET's journals through our Highlighted Trainee Authors program.

Speaking of ASPET's journals, Peer Review Week also occurs this month from September 23–27, 2024. This year's theme, "Innovation and Technology in Peer Review," inspired us to ask some of our Journal Editorial Fellows to share their opinion on the impact of technology on journal publishing, which you can read about in this month's issue. ASPET is incredibly grateful for the time and effort provided by the hundreds (perhaps thousands) of peer reviewers and editors who ensure that *JPET*, *DMD*, *MolPharm*, *PharmRev*, and *PR&P* maintain scientific integrity in everything we publish. As part of that peer review process, ASPET is excited to be partnering with Elsevier on our journals program in 2025, where our peer reviewers and editors will be able to take advantage of the innovation and technological resources provided by Editorial Manager.

Both in September and year-round, ASPET is truly appreciative of everything our postdoctoral members provide to the pharmacology community. Additionally, we are very thankful for the critical impact our peer reviewers have on the entire ASPET journals program.

Dave Jackson, MBA, CAE
Executive Officer, ASPET

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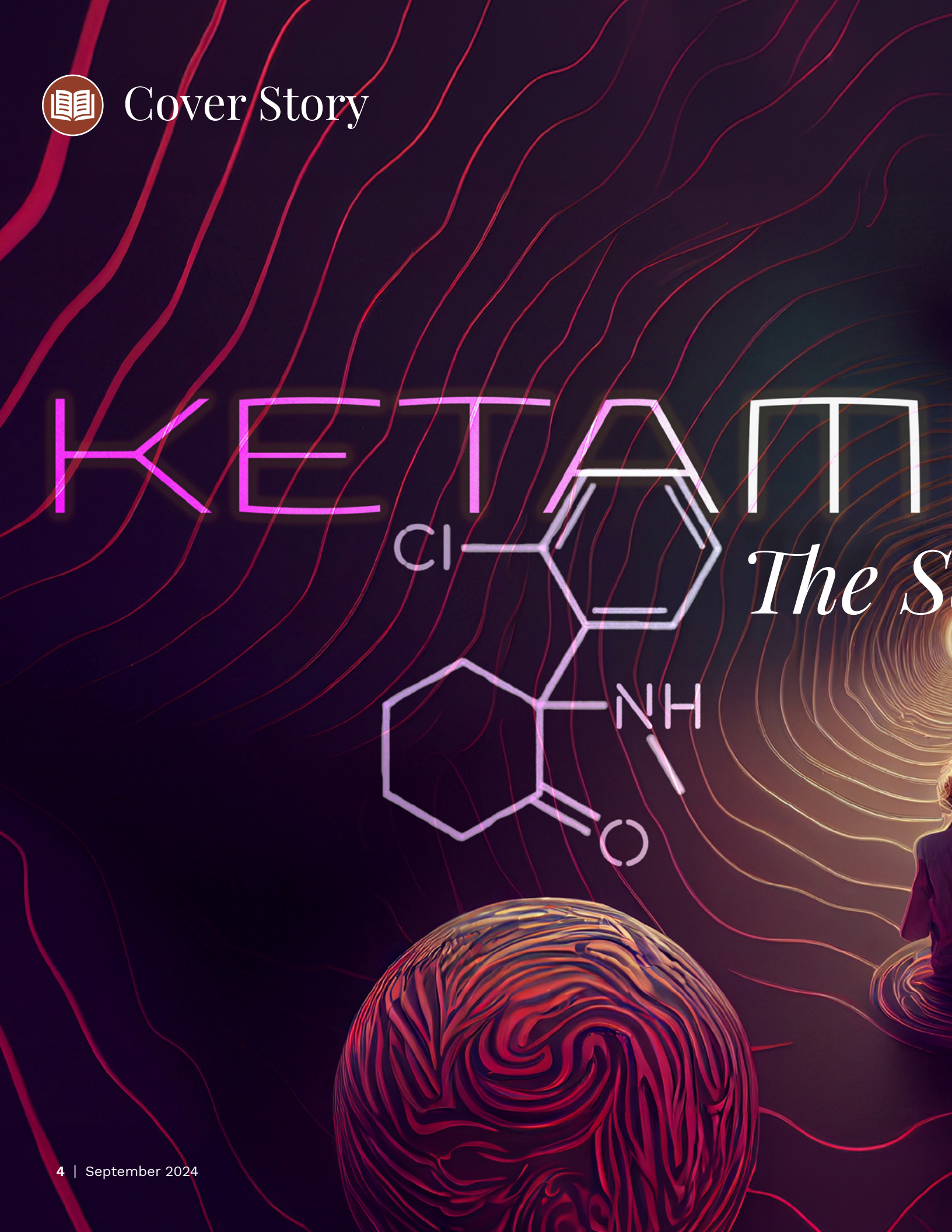

The S

By Rebecca J. Anderson, PhD

Lila Ash had long suffered from depression, and no treatment seemed to help. The few times she felt better, she had taken psychedelic drugs with friends. And yet, when her psychiatrist prescribed ketamine, she hesitated. She considered it a party drug, not a serious medicine. Eventually, though, she reached the point where she was willing to try it.[1]

After resting in a "calming room," Lila was given noise-canceling headphones, an eye mask and a small intramuscular dose of ketamine.[1] Five minutes later, she felt herself "disintegrating," and all her fears and anxiety about ketamine faded away.[1] Gone, too, were her persistent concerns about life. Sadness was replaced with feelings of deep love for her friends, her family and even herself.

When Lila returned to reality (about three hours later), she was no longer burdened with depression. "Because I hesitated to try ketamine," she said, "I suffered longer than I had to. The treatment helped me look ahead with hope for my future".[1]

For the past two decades, ketamine has been on the leading edge of research that is turning psychedelic drugs into clinically beneficial therapies for psychiatric disorders. And most amazingly, ketamine has proven effective in cases that are refractory to conventional therapy.

Too High for Comfort

In the 1950s, scientists at Parke-Davis & Company in Detroit were investigating a series of cyclohexylamines in their search for an "ideal" anesthetic drug with analgesic properties.[2] On March 26, 1956, they synthesized phencyclidine, commonly called PCP.[2,3]

On September 11, 1958, Parke-Davis pharmacologist G. Chen received the compound for testing. Chen, along with Edward Domino, a pharmacologist at the University of Michigan, found that PCP was a potent analgesic in animals.[2] But it also caused the appearance of drunkenness in rodents, delirium in dogs, cataleptic states in pigeons, and anesthesia in monkeys.[3]

When monkeys were given PCP, the researchers could perform surgery without eliciting pain, but the animals' eyes were open, and their muscles had more tone—not less, which is typical of other anesthetics.[2]

Clinical trials were conducted at Wayne State University, and PCP was subsequently marketed as Sernyl®.[2] It proved to be a safe and reliable

latimes.com/opinion/story/2024-02-11/ketamine-treatment-depression-psychedelics

Lila Ash describes her experience with ketamine treatment *(Illustration by Lila Ash / For The Times)*

sciencehistory.org/stories/magazine/old-drug-ketamine-offers-new-hope-for-chronic-pain-sufferers

Edward Domino

Calvin L. Stevens, circa 1955

gf.org/fellows/calvin-l-stevens

clinical anesthetic.[3] Just like in monkeys, PCP was also a potent painkiller and did not depress the patients' cardiovascular or respiratory function.

Unfortunately, PCP's usefulness was limited, because patients experienced postoperative excitation, delirium, and psychotic reactions, which sometimes lasted for hours.[2,3] PCP was removed from the market in 1978. It was eventually classified as a Schedule I controlled substance (i.e., no accepted medical use and a high potential for abuse).

A Milder Shade of High

Despite PCP's psychotic-like properties, Cal Bratton, head of pharmaceutical research at Parke-Davis, was unwilling to give up. He championed continued research, hoping to find an analog without PCP's side effects and abuse potential.[4] Calvin L. Stevens, a professor of organic chemistry at Wayne State University and a consultant to Parke-Davis, synthesized a series of PCP derivatives in his laboratory.[3]

In 1962, Stevens synthesized CI-581.[2,3] Chen and his colleagues at Parke-Davis found that it produced excellent anesthesia in animals. Because CI-581 was a ketone with an amino group, they named it ketamine.[2]

Ketamine was less potent, considerably shorter acting, and most notably, caused less intense psychotic effects than PCP.[2,3]

In early 1964, Parke-Davis asked Ed Domino to study ketamine in humans. Because Domino was not an anesthesiologist, he partnered with Guenter Corssen, a professor of anesthesiology at the University of Michigan who was studying intravenous anesthetics.[2,3]

On August 3, 1964, Domino and Corssen began their clinical trial, recruiting volunteers from the prisoner population at the Parnall Correctional Facility in Jackson, Michigan.[2,3] Intravenous ketamine produced anesthesia and profound analgesia within 1–2 minutes. The effects lasted 5–10 minutes and could be safely prolonged with repeated infusions.[5]

Continued on page 26

Leadership Profile

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A Conversation with ASPET's Young Scientists Committee Chair Saranya Radhakrishnan, PhD

Saranya Radhakrishnan, PhD, is the Chair of ASPET's Young Scientists Committee. In this role she supports the development of future pharmacologists and ASPET members and provides leadership experience to trainees within ASPET. The committee organizes and supports representation of trainees at the committee level, unifies trainees across divisions, and communicates through other committees and with senior ASPET officers. Dr. Radhakrishnan is a Postdoctoral Research Fellow at the National Institute of Mental Health (NIMH) and received her PhD from Purdue University. She has been a member of ASPET since 2019 and also serves on the Animals in Research Policy subcommittee.

Dr. Radhakrishnan discusses her growing involvement with ASPET and the importance of mentoring, with *The Pharmacologist*.

How did you get started in pharmacology?

My research journey has spanned several fields, beginning in bioengineering, and culminating in neuropharmacology. As an undergraduate in bioengineering in India, I had the chance to participate in a semester abroad program, which ignited my passion for research. This experience led me to work in cancer genomics and neurodevelopment as a post-baccalaureate researcher. My interdisciplinary graduate studies further expanded my expertise in neuroscience and chemical biology. Currently, my postdoctoral work at NIMH leverages this chemical biology background to explore neuropharmacology, with a focus on understanding the trafficking mechanisms and regulation of neurotransmitter transporters.

How did you first get involved with ASPET?

During graduate school, I attended Experimental Biology meetings as a member of ASBMB, but I also embraced the opportunity to attend several intriguing ASPET sessions. As my research transitioned into the pharmacology sphere, I was drawn to ASPET's programming and decided to take advantage of the resources and community it offered.

The Washington Fellows program particularly appealed to me as someone interested in science policy, and it ultimately influenced my decision to become an ASPET member. Although I wasn't accepted into the program on my first try, ASPET's welcoming environment encouraged me to stay involved, and I finally had the opportunity to participate in the Washington Fellows program in 2022, which deepened my engagement with the society. Over time, I became more involved, participating in the Animals in Research Science Policy subcommittee, the Young Scientists Committee (YSC) and had the opportunity to chair sessions at the ASPET Annual Meeting.

What do you want the ASPET membership to know about you and your ideas on how to move the organization forward during your term?

As a representative for young scientists, I am committed to fostering a more inclusive and supportive environment for early-career scientists. I believe strongly that access to mentorship, networking, and professional development opportunities will empower young scientists to thrive. My passion lies in expanding networks and mentorship opportunities for early-career pharmacologists within ASPET, ensuring that they have the resources and connections they need to succeed.

I aim to enhance collaboration across ASPET committees, encouraging innovative programming that supports our members at all stages of their careers. The current YSC cohort is particularly enthusiastic and full of ideas for programming designed to support the professional development of early-career researchers, from undergraduates to postdoctoral fellows and independent research scholars. Together, we can create an environment that nurtures the next generation of pharmacologists and advances our field.

What has been your proudest accomplishment in your career so far?

Some of the proudest accomplishments in my career, beyond my scientific contributions during graduate and postdoctoral work, have been mentoring other trainees who have gone on to pursue graduate research careers of their own. I was fortunate to have had supportive mentors throughout my scientific journey, and I'm grateful for the opportunity to now be on the other side of mentorship, helping younger trainees embark on their own research careers.

What advice would you give young scientists who are just starting out in their careers?

To young scientists, I would say: the path ahead is full of challenges, and it's vital to remain resilient and embrace failure as a learning opportunity. Surround yourself with mentors and peers who both support and challenge you. Maintaining a strong support network in your life is crucial and don't hesitate to reach out for help when you need it. As science becomes increasingly collaborative, building and leaning on your network will enhance your career.

Member Highlights

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Professor Paul Czoty, PhD Accepts Vice Chair Role at Wake Forest University

Dr. Paul Czoty, a Professor at Wake Forest University School of Medicine, has accepted the position of Vice Chair in the Department of Translational Neuroscience. Dr. Czoty is a behavioral pharmacologist and neuroscientist with 30 years of experience conducting research using nonhuman primate models of substance use disorder. His research uses brain imaging and behavioral procedures to characterize the abuse-related effects of stimulants and alcohol, separately and in combination. Dr. Czoty has been an ASPET member since 2001.

American Psychological Association's Top Journal Recognizes Adam Prus, PhD

Dr. Adam Prus has received an Editor's Choice Recognition from the American Psychological Association *Journal of Experimental and Clinical Psychopharmacology* for his recently published manuscript titled "Discriminative stimulus properties of two training doses of gabapentin in rats: substitution by pregabalin, diazepam and pentobarbital". This recognition is given to publications that represent the best science in each area of our discipline, reflecting science that is exceptionally important, impactful and deserves additional visibility for the whole field. Dr. Prus is a distinguished Professor and Chair of the Department of Psychological Science at Northern Michigan University and became an ASPET member in 2017.

Graduate Students & Postdoctoral Scientists:

Do you need some help planning your future? Do you have all the skills you need to succeed? Are you trying to decide among careers in academia, government, or industry?

Learn more

Nina Beltran Selected to Prestigious Diversity Program

Nina Beltran has been selected to participate in the Scientist Mentoring and Diversity Program (SMDP) for Biotechnology. This prestigious career mentoring program pairs diverse early-career individuals with mentors with careers in the pharmaceutical, medical technology, biotechnology and consumer healthcare industries. Nina is a doctoral student of the Department of Psychology at the University of Texas at El Paso where she is training with Dr. Katherine Serafine. Nina is considering a career in pharmaceutical sciences and as a SMDP Scholar, she looks forward to learning about industry opportunities and gaining the background to achieve her long-term career goals while enhancing diversity in the biotechnology industry. Beltran joined ASPET in 2018 and was named a 2024 ASPET Washington Fellow.

UMich Appoints Emily Jutkiewicz, PhD First Pfizer Upjohn Research Professor

The University of Michigan has appointed Dr. Emily Jutkiewicz as the inaugural Pfizer Upjohn Research Professor of Translational Pharmacology. Dr. Jutkiewicz is the Past Chair of the Division for Behavioral Pharmacology and joined ASPET in 2006. She is an Associate Professor of Pharmacology and Associate Chair for Education in the Department of Pharmacology in the University of Michigan Medical School. Dr. Jutkiewicz's research program has made important contributions to our understanding of opioid mechanisms contributing to analgesia and depression, the role of endogenous opioid peptides in psychiatric disease states, and delta opioid receptor pharmacology. In addition to leading a productive research program and providing outstanding mentorship to trainees, Dr. Jutkiewicz provides outstanding service to the Department of Pharmacology, the Program in Biomedical Sciences, and Rackham Graduate School as Associate Chair for Education in Pharmacology and Chair of the Pharmacology Graduate Program and Pharmacology Education Leadership Committees.

Advocacy Impact

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This month *The Pharmacologist* features two new policy briefs written by participants of the 2024 ASPET Washington Fellows program. These topics present compelling arguments for policy improvements on an issue of personal importance to each Fellow. The policy briefs below discuss the importance of understanding polysubstance use and accessible treatments for opioid use disorder in El Paso, Texas.

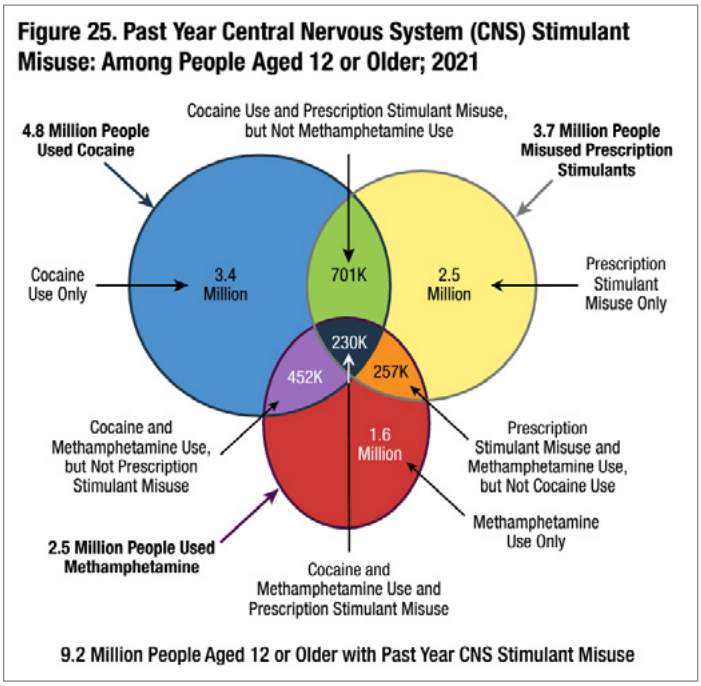
We Are More Than an Isolated Event: Why Polysubstance Use Needs the Spotlight

By Sarah Melton, Louisiana State University Health Sciences Center

Executive Summary

From taking daily maintenance medications, antibiotics, vapes, over-the-counter medications, and pain killers to individuals who struggle with Substance Use Disorder (SUD); people do not administer only one type of medication for their entire life. Nevertheless, why is research conducted like we do? With nearly half of drug overdose deaths involving multiple drugs in 2022 and 250 Americans losing their lives to drugs every day, this is of great importance to Americans at the local, state and federal level.[1,2] National public health initiatives are needed to educate the public on polysubstance use as well as destigmatize seeking help for SUD and polysubstance abuse. Additionally, I propose that federal policy makers set up opportunities for polysubstance research to be highlighted within already existing avenues of funding. Finally, Congress should create a committee that focuses on polysubstance use, research, funding, and education.

Background

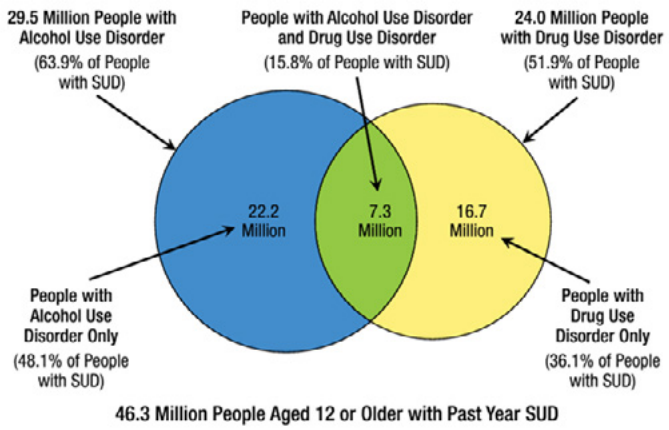


On a personal level, many Americans manage multiple medications throughout their lifetime; often combining over-the-counter medications with other drugs used to treat asthma, high cholesterol, antibiotics and steroids for infections, vaping, birth control, etc...

This polypharmacy extends across various conditions, including post-surgery, chronic diseases, and cancer treatment. According to the Centers for Disease Control and Prevention polysubstance use is defined as, "The use of more than one drug at a time. This includes when two or more are taken together or within a short time period, either intentionally or unintentionally."[2] While genetic influences on prescription drug interactions are studied, little attention is given to the interactions between drugs of abuse, prescribed medications, and over-the-counter drugs. In the healthcare system, most physicians attempt a delicate balance of prescribing multiple medications with a cursory understanding of the downstream side effects. Consequently, there is a large gap in knowledge of polysubstance use from the bench to the bedside. Without proper research and education, the gap widens daily.

On a national level, while publicly navigating through the COVID-19 pandemic, the silent opioid epidemic persists in the U.S. Drug-related emergency visits reached 7.7 million in 2022, with alcohol, opioids, and cannabis being the most common substances involved.[3] Alcohol was the most commonly reported substance in polysubstance-related emergency department visits, often being combined with cannabis, cocaine, and methamphetamine.[4] Over 48.7 million Americans experienced a substance use disorder in the past year, with polysubstance use contributing to over 21% of drug-related emergency visits.[5] Alcohol and opioids are particularly prevalent, with 16,425 deaths from prescription opioid overdose in 2021 alone.[6] According to Crummy and colleagues, polysubstance use is consistently associated with worse treatment outcomes, including poorer treatment retention, higher rates of relapse, and a three times higher risk of mortality compared to using only one substance.[7] While steps are being taken to research each type of SUD individually, there is a greater need to study, learn, and treat polysubstance use and polysubstance use disorder.

Figure 32. Alcohol Use Disorder and Drug Use Disorder in the Past Year: Among People Aged 12 or Older with a Past Year Substance Use Disorder (SUD); 2021



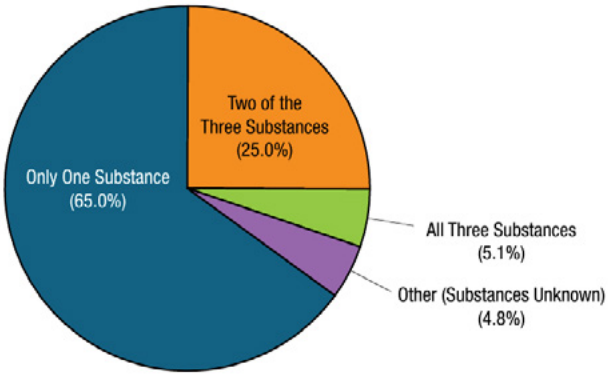
Note: Drug Use Disorder includes data from all past year users of marijuana, cocaine, heroin, hallucinogens, inhalants, methamphetamine, and prescription psychotherapeutic drugs (i.e., pain relievers, tranquilizers, stimulants, or sedatives).

The current data poorly and superficially addresses the complex web of substances prescribed over an individual's lifetime, let alone those mixed for recreational purposes. Understanding the interactions between these drugs, their sequence of introduction, and effective treatment strategies is crucial. Substance abuse imposes significant societal costs, affecting consumers, employers, taxpayers, and economic growth. According to the Health Policy Institute:

> *"Everyone pays for the costs of substance abuse. This includes higher prices for goods and services, increased health insurance premiums, and higher taxes for healthcare, law enforcement, and prevention and treatment programs. Substance abuse also diverts resources from future investments and contributes to the need for foster care and homeless shelters."*[8]

To frame SUD in the appropriate context, this is a medical, research, and public health issue.

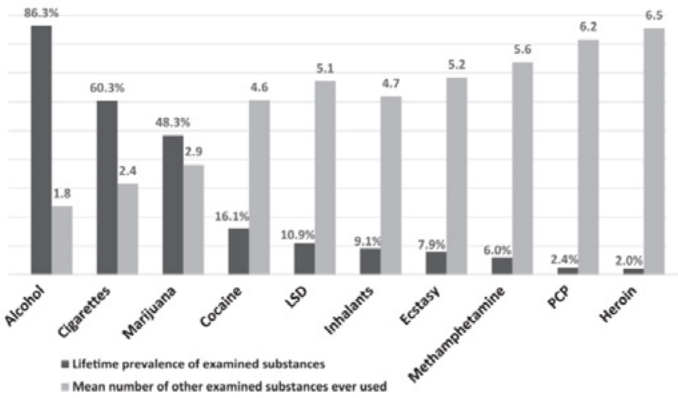
Figure 13. Type of Vaping Use: Among Past Month Users Aged 12 or Older Who Vaped Any Substance; 2021



Note: People who vaped any substance could have used vaping devices to vape substances other than nicotine, marijuana, or flavoring.

Note: The percentages may not add to 100 percent due to rounding.

Fig. 1: Overlap of substances used across the lifetime.



Weighted lifetime prevalence of substance use and mean number of other substances ever used by adults age 18 and older in the United States (n = 51,000; Source: 2018 U.S. National Survey on Drug Use and Health [adapted from Eric Wish, University of Maryland, Center for Substance Abuse Research]).

Instead of focusing solely on restricting access to addictive substances, collaborative efforts across medicine, research, public health, and policy should aim to develop innovative therapies; to expand treatment options, promote harm reduction strategies, and combat stigma through education and evidence-based interventions. This collaborative strategy can reduce the number of emergency department visits and drug overdoses in the U.S., ultimately improving public health outcomes and societal well-being.

It is imperative to recognize that approximately 92.4% of individuals with lifetime substance use also report lifetime use of alcohol or illicit drugs.[9] This statistic underscores the interconnected nature of substance use and the need for comprehensive approaches to treatment and intervention. While efforts to understand and address individual substance use disorders are important, addressing polysubstance use offers a broader perspective on the complexities of addiction and substance misuse. Thus, investing in research and treatment strategies specifically tailored to polysubstance use is essential for mitigating its impact on American public health.

Policy Recommendations

I propose a multifaceted approach to address the pressing and complex issue of polysubstance use and abuse:

- *National and state-level public health initiatives are essential to educate the public about polysubstance use.* Focusing efforts to destigmatize seeking help for substance use disorder, promote harm reduction strategies, and combat stigma through evidence-based interventions. Through collaborative efforts, we can decrease emergency department visits and drug overdoses in the U.S., thereby enhancing public health outcomes and societal well-being.
- *Establish direct funding channels for polysubstance research through already existing federally funded grants.* This can be achieved by either creating specialized study sections within existing grant processes or incorporating a dedicated section in grant proposals where researchers can articulate the potential impact of their work on polysubstance use and vice versa. The NIH HEAL initiative or NIDA could spearhead this endeavor to spread across multiple other federal agencies to recognize under-funded research opportunities.

- *Create a House of Representatives committee specifically focused on polysubstance research.* This committee could operate in conjunction with the Science and Space Technology Committee, providing a structured platform for policymakers to delve into the intricacies of polysubstance issues. With over 56 caucuses touching upon polysubstance use in some capacity, it is evident that this is a pervasive issue requiring dedicated attention and advocacy from top policy makers.

By adopting these measures, we can foster a comprehensive and collaborative approach to addressing polysubstance use; ensuring that research, policymaking, and public awareness efforts are effectively coordinated to relieve the adverse effects of this complex issue.

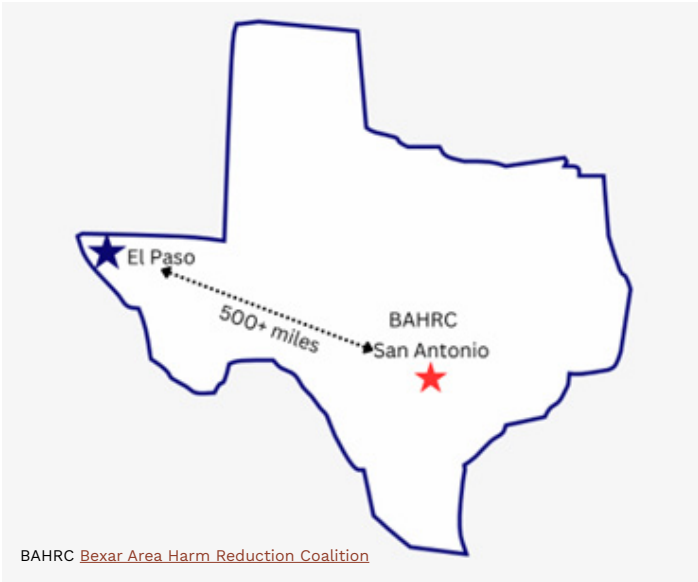
References can be found on page 37.

Accessibility of Treatments for Opioid Use Disorder in El Paso, Texas

By Nina Beltran, The University of Texas at El Paso

Executive Summary

Opioid drugs such as fentanyl, oxycodone, and heroin contributed to nearly 87% of all drug-related mortalities in 2021. Opioid reversal drugs (e.g., Narcan) and syringe service programs exist to prevent opioid-related mortalities. In El Paso, Texas, police officers are not required to carry Narcan. In addition, the closest syringe service exchange program in San Antonio, Texas, is located over 500 miles away. To improve the accessibility of treatments and services for opioid use disorder in El Paso, Texas, policymakers should focus on necessitating training and accessibility of Narcan to first responders and expand existing syringe service programs to El Paso, Texas.



BAHRC Bexar Area Harm Reduction Coalition

Background

Opioids are a class of drugs naturally derived from the opium poppy plant.[1] Opioids can be semisynthetic or synthetic, as they are made in a laboratory. Prescription opioids, such as morphine, hydrocodone, and oxycodone, are

prescribed to treat pain-related conditions.[2] These drugs act on the brain reward pathway, producing euphoria.[2] Taking these drugs chronically to treat pain-related conditions or to achieve euphoria can be problematic, as this increases the risk of drug misuse and can lead to opioid use disorder.[3] Opioid use disorder is characterized by symptoms such as taking larger amounts of drug over a longer period than intended, craving or a desire to use opioids, the need to increase the amount of drug to achieve a desired effect, or experiencing withdrawal symptoms from opioids.[4] While opioid withdrawal is not fatal, it does cause side effects that create a significant motivation to continue opioid use to prevent withdrawal.[5]

A recent national survey reported that nearly 2.5 million individuals in the U.S. have opioid use disorder.[6] Further, opioids contributed to nearly 75% of all drug overdose deaths in 2020. In just one year, in 2021, this number jumped to nearly 87% of drug-related mortalities.[4] Treatments are available for opioid use disorder; however, only 1 in 5 people with opioid use disorder receive treatment. This can include counseling, behavioral therapies, and medication treatment.[7] These medications include methadone, which reduces cravings but is only available in regulated clinics. Buprenorphine is prescribed as a replacement for opioids. In addition, naloxone, also known as Narcan, is used in emergencies to reverse opioid overdose when a person is experiencing respiratory depression.[8] While these treatments exist, treatment works best when personalized and accessible to the individual.

Individuals seeking treatments may experience barriers or a lack of accessibility. This can include the absence of health insurance in the limited number of facilities offering treatment services.[9] Further, certain populations are reported to be less likely to receive treatment, which includes black adults, women, and unemployed individuals.[6] However, in March of 2023, the FDA approved Narcan, a nasal spray, for purchase over the counter and approved for use without a prescription.[10] While this may be accessible to some, it may not be accessible to all. To fill this gap, harm reduction offers an opportunity to reach people who may not have access to or cannot afford this care. Examples include syringe services programs or syringe exchange programs that provide access to sterile needles and syringes, facilitate safe disposal of used syringes, and provide referrals for treatment programs.[11]

El Paso, Texas, has a population of nearly 700,000, of which 81% is Hispanic.[12] In El Paso, Texas, there are no syringe service programs; in all of Texas, only one program is available located over 500 miles away in San Antonio, Texas.[13,14] In 2021, there was a 50% increase in opioid-related mortalities in El Paso, Texas, resulting in 101 fentanyl-related deaths.[15] First responders, such as police officers in El Paso, Texas, are not required to carry the lifesaving reversal drug Narcan.[16,17] Research supports that increasing someone's chance of surviving an overdose, the sooner Narcan should be administered.[18] Making Narcan accessible to people in the community and first responders is critical to improving outcomes. Specifically, in other states, it has been reported that police officers carrying Narcan results in a reduction in overdose deaths.[19] These findings indicate the effectiveness of these practices in mitigating opioid overdoses. There is currently one non-profit organization in El Paso, Texas, known as Punto de Partida, that provides harm reduction resources such as fentanyl test strips, Narcan, and hygiene kits.[20] While this organization provides beneficial resources, the stigma of addiction is highly prevalent among Hispanic populations[21], which may contribute to the lack of treatment accessibility and barriers to training resources in the community.

Texas policymakers should allocate funding for the service programs located in San Antonio, Texas, to allow expansions of other programs in Texas, including El Paso, Texas. This expansion should include programs targeting education to decrease the stigma and discrimination of drug use. Further, these programs should include resources such as safe disposal of used syringes, fentanyl test strips, and Narcan distribution to minimize self-harm and improve recovery to mitigate existing barriers to treatment and other resources. In addition, Texas policymakers should require first responders, including police officers, to carry and have training on lifesaving reversal drugs, such as Narcan. While emergency medical services (EMS) typically fulfill this role, if police officers respond and arrive at an emergency before EMS, they should have the training and the resources to treat opioid overdoses with Narcan. While treatments for opioid use disorder are accessible to some, this is not accessible to all, especially to those in case of an emergency in El Paso, Texas.

References can be found on page 38.

Interested in Being a Contributing Writer?

ASPET's *Pharmaco Corner* blog and award-winning flagship magazine *The Pharmacologist* seek contributing writers on a rolling basis.

PHARMACO CORNER

Discussing Science. *Discovering* Cures.

Pharmaco Corner is a dedicated space where pharmacology experts can discuss issues that affect them professionally and personally. The blog connects science and society through various pharmacology disciplines. Send your pitches to pharmacocorner@aspet.org.

The Pharmacologist

The Pharmacologist wants writers interested in contributing human interest and science stories focused on pharmacology. Contact us at thepharmacologist@aspet.org. Please include links to writing samples.

On Their Way...

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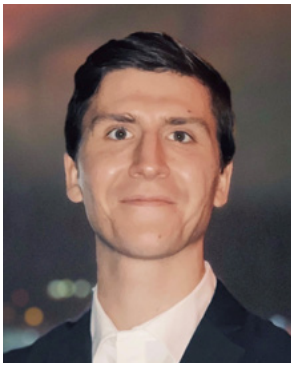
Each month, the editors of three of the American Society for Pharmacology and Experimental Therapeutic's (ASPET) journals choose who they call their Highlighted Trainee Authors. These early-career scientists are recognized for their innovative research published in *The Journal of Pharmacology and Experimental Therapeutics*, *Drug Metabolism and Disposition*, and *Molecular Pharmacology*. This feature showcases selected young scientists, demonstrates what drives them and reveals why pharmacology is important to them.



Remi Janicot

"During my early education, I had a fascination for science and enjoyed the challenge of understanding the complexity of how the human body worked," explained Remi Janicot, a fourth-year PhD student. After receiving his bachelor's degree in Neuroscience, he was torn about his next step. So, to gain a better understanding of life as a researcher, he joined the lab of Carl Stafstrom as a lab technician at John's Hopkins Medical School researching the mechanisms underlying pediatric epilepsy.

"It is there that I made my first real scientific contributions and decided to pursue this path by joining the PhD program at Boston University Chobanian & Avedisian School of Medicine," Janicot said.

His interest in science was influenced by his father who has a PhD in Biochemistry and worked his entire career in the pharma and biotechnology industry. Janicot said he was never pushed to follow his father, but he's "sure that overhearing his discussions about his work sparked some interest in science from an early age."

He also credits Dr. Mikel Garcia-Marcos who encouraged him to attend scientific meetings (like the ASPET Annual Meeting) from an early stage in his PhD. Janicot considers his attendance as foundational experiences for his development as a scientist. Having attended multiple ASPET annual meetings, Janicot says that he's fully aware of the quality of the work that this community delivers.

"The members that make up ASPET journals are all accomplished scientists with high standards, with deep ties to the pharmaceutical industry which plan to join," Janicot said. "To get published in an ASPET journal and get this recognition is a great personal accomplishment, but also a testament to the quality of the work that goes on in the Garcia-Marcos lab and in the Biochemistry & Cell Biology Department at Boston University." Janicot's research article is now available in the September issue of *Molecular Pharmacology*.

Yu Wang

Yu Wang, PhD, received his doctorate degree in Pharmacokinetics at the College of Pharmaceutical Sciences, Zhejiang University and will begin working as a postdoctoral researcher focusing on

PK-related projects. Early in his career he's been drawn to pharmaceutical sciences.

"Since my undergraduate studies, I have majored in pharmaceutical sciences," Wang said. "I realized that pharmacology, particularly pharmacokinetics, plays a pivotal role in new drug development, drug dosage adjustment and safe usage of drugs in the clinic." This realization led him to pursue graduate study under supervision of Prof. Zeng, a renowned expert in this field.

Although he was drawn into nanomedicines in a short period, "Prof. Zeng's influence convinced me to continue focusing on PK and made me fascinated by it," said Wang. Meanwhile, he aims to deepen his knowledge and skills in this area.

"ASPET publishes several esteemed journals that feature articles on pharmacology-related areas and presents them to the pharmacists or researchers actively engaged in the discipline. Publishing an article in the journal means that our work could contribute valuable research insight as well as experiences to this field, and it might also help to expand the corpus of knowledge in PK," Wang explained.

In addition to having his work published in the September issue of *Drug Metabolism and Disposition*, Wang plans to be a teacher at university, teaching PK courses and exploring the alteration of pharmacokinetic properties of drugs in specific patients using molecular biology.

Upcoming Events

2024 ACCP Annual Meeting
October 12–15, 2024 · Phoenix, AZ

Join your peers at the 2024 ACCP Annual Meeting!

British Pharmacological Society Pharmacology 2024
December 10–12, 2024 · Harrogate, North Yorkshire

Network and hear the latest developments and research in pharmacology from industry experts and emerging investigators.

ASPET 2025 Annual Meeting
April 3–6, 2025 · Portland, OR

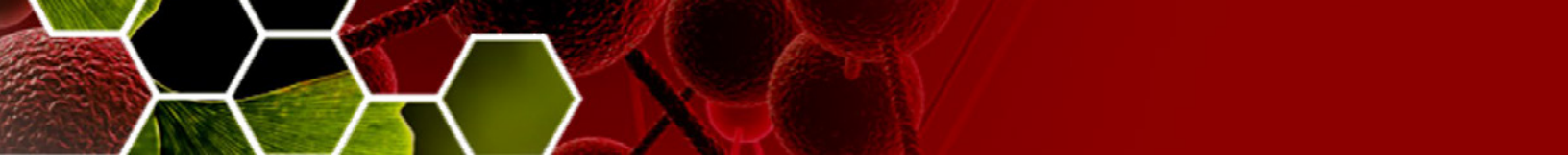
Advancing the Science of Drugs and Therapeutics. Join us in Portland!

ASPET 2026 Annual Meeting
May 17–20, 2026 · Minneapolis, MN

Join us in Minneapolis!

20th World Congress of Basic and Clinical Pharmacology 2026
July 12–17, 2026 · Melbourne/Narrm, Australia

We will welcome the world's pharmacology and therapeutics community to the Melbourne Convention Centre in Melbourne/Narrm, Australia.



The 2024 ASPET-GLC Annual Meeting in Review

Share this!

The 37th Annual Meeting of the Great Lakes Chapter of the American Society for Pharmacology and Experimental Therapeutics (ASPET-GLC) was held at Rosalind Franklin University of Medicine and Science (RFUMS) in North Chicago on June 21, 2024. More than 165 pharmacologists, neuroscientists, biologists, clinicians and students attended the meeting. They represented academia and the pharmaceutical industry in the Midwest, including 24 ASPET members.

This year's conference theme, "Advances in Pharmacology and Neurobiology of PTSD and Anxiety Disorders," highlighted recent advances in the neurobiology and pharmacology of post-traumatic stress disorder (PTSD) and anxiety disorders. Keynote speaker Ann Rasmusson, MD of Boston University and the VA National Center for PTSD, gave a presentation entitled, "Incorporating the Neurobiology of PTSD into Treatment Development: Serendipity versus Design."

The symposia also featured various nationally- and world-renowned experts in the fields of pharmacology and neuroscience of PTSD and anxiety disorders. The presenters evaluated novel pharmacological strategies for these conditions, including the use of psychedelics, neuropeptides, and inhibitors of enzymes which metabolize cannabinoids in the human body. Data were presented from human studies as well as preclinical data in animal models and cell culture. In addition, the neurobiology sessions discussed advances in our understanding of these disorders, which may be explored in future drug developments.

Main Symposium speakers included Amiel Rosenkranz, PhD (RFUMS, "Stress Dampens Prefrontal Cortical Regulation of Amygdala in Rats"); Sachin Patel, MD, PhD (Northwestern University, "Targeting Endogenous Cannabinoid Signaling for Stress and Trauma-Related Disorders"); and Leah Mayo, PhD (University of Calgary, "The Highs and Lows of Exploring the Endocannabinoid System as a Novel Therapeutic Target in the Treatment of PTSD: Evidence from Clinical Populations").

The Young Investigator Symposium featured early-career faculty who shared their science. Speakers included Nicole Ferrara, PhD (RFUMS, "Developmental Differences in Fear Elevation and Supporting Neural Circuitry"); Hao Li, PhD (Northwestern University, "A Neuropeptidergic Mechanism Directing Behavioral Selection Under Conflicts"); and Hanna Molla, PhD (University of Chicago, "Effects of Low Dose LSD on Negative Mood States in Mildly Depressed Individuals").

Fifty-four posters were presented at the poster session featuring a wide variety of subfields, including studies evaluating the efficacy of new pharmacological agents, and studies elucidating novel pathophysiological mechanisms underlying disease. As part of GLC's mission to promote the benefits of ASPET membership

to early-career scientists in the Midwest, all trainees who placed in the poster competition received complimentary membership to ASPET. Also, as part of our membership drive, an additional seven attendees joined ASPET after the meeting.

The Lunch and Learn events provided many opportunities for cross-disciplinary collaboration and learning. In the new event, Researcher-Clinician Connection, scientists who study mental health disorders were grouped with clinicians who treat these disorders. Many of the participating clinicians were affiliated with the Lovell Federal Health Care Center, the only VA hospital in the country that serves active military members and veterans.

The Career Development Workshop offered the opportunity for trainees to learn about various biomedical careers with mentors from AbbVie and RFUMS. Faculty mentors shared

their experiences on the process of obtaining a university position, of being the founder of a biotech startup company, and being an advocate for science policy in the government. AbbVie mentors included a medical writer, a safety pharmacologist and an industry postdoctoral fellow.

In the Chicagoland Pharmacology Educator Symposium, pharmacology faculty from a variety of healthcare or research PhD programs discussed best practices for pharmacology education. Lastly, a tour of the Innovation and Research Park introduced attendees to RFUMS' Helix 51, the only incubator in Lake County, Il. for biomedical start-ups and early-stage and international companies.

This meeting was co-sponsored by the Center for the Neurobiology of Stress Resilience and Psychiatric Disorders at RFUMS. Thirteen universities, two healthcare centers, and four pharmaceutical or biotech companies were represented at the meeting. To get more involved in the ASPET Great Lakes Chapter, follow us on Facebook and LinkedIn or contact the GLC President Dr. James O'Donnell.

Journals Highlights

Share this!

Peer Review Week: Innovation and Technology in Peer Review

ASPET acknowledges the vital contributions of its peer reviewers across its five journals. They work diligently to maintain the journal review process and elevate the important science published on pharmacology and experimental therapeutics. According to the Society for Scholarly Publishing, Peer Review Week is a globally recognized, annual, community-led, virtual event that celebrates the indispensable role of peer review in upholding research quality.

This year's celebration will be held between September 23–27, 2024, and the theme is "Innovation and Technology in Peer Review." To engage with this theme and to start what we hope will be a deeper conversation, ASPET asked this question to members of the 2024 *JPET* Editorial Fellows:

What do you think the impact of innovation and technology will be on the evolving publishing landscape?

Here's what some of the fellows had to say:

"I think that Artificial Intelligence (AI)-driven tools are a double-edged sword, bringing both opportunities and challenges to the peer review process. They can streamline the workflow by assisting editorial board members and peer reviewers with screening journal submissions, detecting plagiarism, and finding peer-reviewers, thus reallocating time for scientific evaluation and reducing the workload-related delays. AI can also enhance inclusivity and diversity by supporting non-native English authors and peer reviewers. On the other hand, AI tools can introduce inaccuracy and biases and make research misconduct easier. Responsible and ethical use of AI has the potential to serve scholarly publishers and the scientific community at large."

Marie-Noëlle Paludetto
Postdoctoral Researcher, University of Manchester

PEER REVIEW WEEK

What do you think the impact of innovation and technology will be on the evolving publishing landscape?

Here's what some of the fellows had to say:

"Innovation and technology are poised to transform the publishing landscape by improving the efficiency and precision of the editorial process, resulting in a shorter submission-to-decision timeline. Advanced AI tools can quickly identify data manipulations and ensure compliance with journal guidelines. Additionally, these tools can optimize the reviewer selection process by verifying expertise and detecting potential conflicts of interest, ultimately enhancing the quality and integrity of published articles."

Khaled Abdelrahman, BPharm, PhD
Assistant Professor, University of British Columbia

"The impact of innovation and technology on the publishing landscape is transforming and multifaceted. For audiences, these advancements enable the creation and distribution of interactive materials, such as e-books, audiobooks, podcasts, and social media content. This not only efficiently improves global access to knowledge and information, but also significantly enhances our reading experiences, making it more interesting, engaging, and immersive, particularly for educational and practical content.

For writers, AI tools, such as ChatGPT, are increasingly employed to create content in multiple aspects, from writing and idea generation to article translation and editing. This allows human writers to focus on creative and communicative jobs, freeing them from repetitive, laborious, and time-consuming tasks.

For publishers and platforms, AI-assisted algorithms provide personalized recommendations and services to potential readers, reaching targeted audiences and customers more effectively and extending the media marketing through new business models.

While technology offers unprecedented opportunities, careful consideration is needed to address current challenges related to ethics, information quality, and accessibility; and traditional publishers must adapt to rapidly changing market dynamics, balancing technological innovations with established practices to deliver the best services to their customers."

Qingxiang (Nick) Lin, PhD
Postdoctoral Research Fellow, Massachusetts General Cancer Center and Harvard Medical School

NATIONAL * POSTDOC APPRECIATION * WEEK

SEPTEMBER 16 - 20, 2024
WWW.NATIONALPOSTDOC.ORG/2024NPAW
@NATIONALPOSTDOC

At ASPET, postdocs and early-career scientists in general are active and welcome members of the Society. With their enthusiasm, innovative ideas and outstanding commitment to advancing the field of pharmacology, ASPET is stronger with their involvement. For National Postdoc Appreciation Week, we recognize, celebrate and appreciate all the early-career scientists who call ASPET home and we encourage postdocs to join the ASPET community.

ASPET
Transforming Discoveries into Therapies

Continued from page 7

The prisoners described vivid dreamlike experiences, the sensation of floating in outer space, and no feelings in their limbs. This altered state of consciousness as well as the post-surgical delirium were minimal compared to PCP. Respiratory depression was slight, and the prisoners exhibited modest increases in blood pressure and heart rate.[5]

As Domino and Corssen were writing their results for publication, they had long discussions about how to describe the novel ketamine effects on consciousness. They considered "schizophrenomimetic" and "dreaming".[2] Then, one evening, Domino described the effects to his wife, Toni, explaining that the men seemed "disconnected." She suggested the term, "dissociative anesthetic." Beginning with Domino and Corssen's 1965 paper, ketamine (and subsequently other drugs in this class) has been described as a dissociative anesthetic.[5]

More recent electrophysiological and functional studies have found that "dissociative" drugs disrupt the connections between the brain's thalamo-cortical and limbic systems.[2]

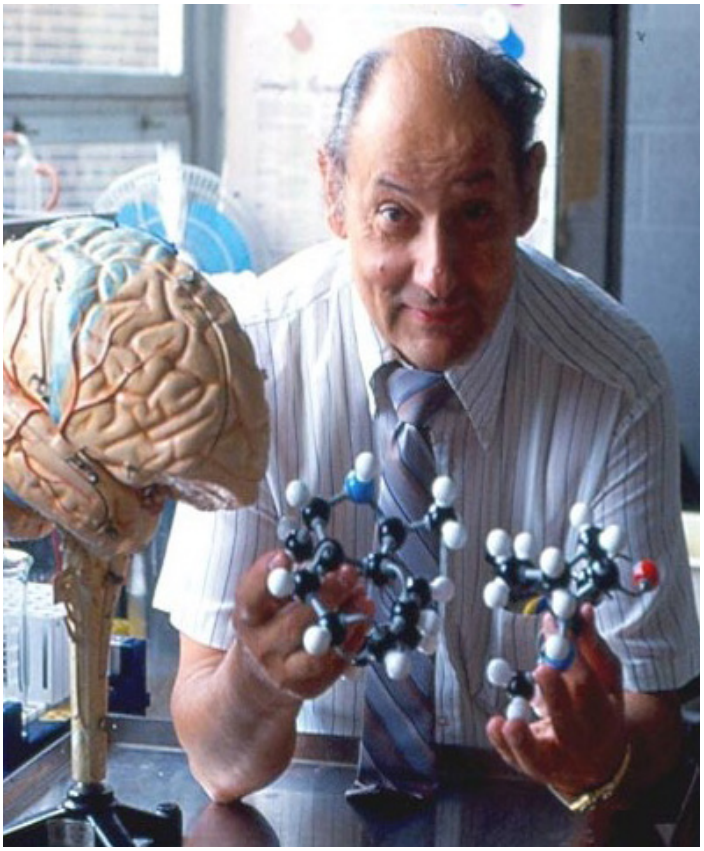
> ***One evening, Domino described the effects [of ketamine] to his wife, Toni, explaining that the men seemed "disconnected." She suggested the term, "dissociative anesthetic."***

A Unique Anesthetic

Domino and his colleagues at the University of Michigan continued to study the pharmacology of ketamine.[2] Its effects were quite distinct from all other anesthetics. Instead of depressing cardiovascular function, ketamine increased blood pressure, heart rate, and cardiac output.[6] Ketamine caused only modest respiratory depression. Interestingly, it was also a potent bronchodilator with the unique ability to preserve upper airway reflexes. But it induced copious salivation, which in rare cases risked laryngospasm.[3,6]

Patients under ketamine-induced anesthesia were unresponsive to commands, but their eyes may have remained open. Their limbs moved involuntarily and, like with PCP, their muscle tone was increased.[6]

Parke-Davis patented ketamine in the US in 1966. It became available by prescription in 1969 under the trade name Ketalar® for



medicine.umich.edu/dept/domino-research-center/message-director

Edward Domino

veterinary use and was widely used for surgical anesthesia in animals.[2,6] The Food and Drug Administration (FDA) approved ketamine (Ketalar) for human use in 1970.[2,3]

Ketamine is water and lipid soluble and can be safely administered intravenously, intramuscularly, subcutaneously, nasally, orally, and by other routes.[3]

Because of its rapid onset, short half-life, and impressive safety profile, ketamine became a popular induction anesthetic in a variety of patient populations and settings. Slow intravenous infusion minimized postoperative agitation.[2,3]

Ketamine was a popular battlefield anesthetic in Vietnam.[2,3,7] Because it can be used safely in patients with elevated intracranial pressure (and may in fact be neuroprotective), ketamine was used in patients with traumatic brain injury.[3,8] Its benefits included protection against seizures, cerebral ischemia, and secondary brain injury due to hypotension, and it continues to be used in military trauma medicine.[3]

Ketamine's pharmacological properties and ease of use also made it a safe and effective anesthetic option in emergency field settings, such as mass casualty events.[3,8]

A Potent Painkiller

Ketamine provides a form of pain relief quantitatively and qualitatively similar to opioids.[3,4] Unlike opioids, though, ketamine produces its analgesic effect while maintaining cardiopulmonary stability, airway reflexes, and respiratory function.[2,3]

Sub-anesthetic intravenous doses (0.2 to 0.8 mg/kg) produce good analgesia and sedation, and slow sub-anesthetic infusions

ketamine.com/history-of-ketamine/timeline-of-the-history-of-ketamine

Ketamine was used as an anesthetic for soldiers in the Vietnam War

(0.5 mg/kg per hour) produce continuous analgesia and sedation. Long-term infusion of a sub-anesthetic dose (10–40 mg per hour for 5 days) has been effective in relieving the pain of patients suffering from complex regional pain syndrome.[4]

Ketamine infusions may also provide an opiate-sparing alternative for managing post-operative pain and the pain of cancer patients who otherwise require high-dose opioids. It is also increasingly used as an adjunct for chronic pain. There are reports of efficacy in phantom limb pain, fibromyalgia, ischemic pain, and migraine with aura.[3]

In burn patients, ketamine provides analgesia and sedation during debridement, grafts, and repeated dressing changes, without compromising the patient's airway or respiratory function.[3]

Finally, the convenience of intramuscular administration, along with the wide safety margin, made ketamine one of the most commonly used drugs for sedation and analgesia in children, in emergency department patients, and in other uncooperative patients. Emergence excitability in children and teenagers is rare and typically mild.[3]

Efforts to explain the mechanisms underlying ketamine's actions are providing researchers with new insights into the relationship between consciousness, anesthesia, and analgesia.[3]

Unlike most other anesthetics, which act primarily through potentiation of GABA transmission, ketamine has many molecular targets and neurophysiological properties.[3]

It reportedly interacts with NMDA, dopamine, serotonin, sigma, opioid, and cholinergic receptors, as well as hyperpolarization-activated cyclic nucleotide-gated channels.[4]

Its anesthetic effects are generally attributed to inhibition of N-methyl-D-aspartate (NMDA) receptors.[4] There also appears to be a direct action on mu and delta opioid receptors (similar to morphine).[4,9] Ketamine's effect on pain seems to be mediated through both antagonism of NMDA receptors and activation of mu opioid receptors.[4,9,10]

Let's Party

By the mid-1970s, ketamine gained additional popularity. Soldiers returning from Vietnam brought along their experiences with ketamine, leading to widespread recreational use in the U.S.[2,4,11] In this wilder chapter of ketamine, sub-anesthetic shots became popular among psychedelic drug enthusiasts.[10] Known on the street as "Special K," ravers and other partiers were attracted to the swirly, out-of-body sensation that the drug produced.[2,3,7,10–12]

The "high" from a small intravenous infusion of ketamine was characterized by hallucinations and a distortion of time and space.[3,4] Higher doses induced more severe, schizophrenia-like symptoms and perceptions that were completely separate from reality.[3]

Because of its potential for abuse, ketamine was classified as a Schedule III controlled substance in 1999 (i.e., moderate to low potential for physical and psychological dependence).

Testing at Yale

In parallel, a smattering of investigators suggested that ketamine might have antidepressant effects.[2] The well-established standard-of-care for patients with major depression was a group of drugs that all targeted monoamine neurotransmitters. Those drugs were effective in many cases, but they caused a variety of unpleasant side effects. And sadly, about one-third of patients with major depressive disorder failed to respond.[7,13–15]

One alternative was electroconvulsive therapy, which was usually effective when antidepressant drugs failed, but not always.[8,16]

In the late 1990s, several lines of evidence suggested that dysfunction of the glutamatergic system might play an important role in depression.[7,17,18] This prompted Dennis Charney and his team at Yale to explore whether ketamine (because it targets the glutamatergic NMDA receptor) possessed antidepressant properties.[2,7]

They enrolled seven patients who had not responded to standard antidepressants, a condition now generally called "treatment-resistant depression".[18] A sub-anesthetic dose of ketamine was infused intravenously. To Charney's surprise, the patients felt better just hours after the infusion, and their depressant symptoms significantly decreased within 3 days after the single-dose treatment.[18]

To Charney's surprise, the patients felt better just hours after the [intravenous ketamine] infusion, and their depressant symptoms significantly decreased within 3 days after the single-dose treatment.

The trial was double-blinded, but the investigators admitted that patients were able to discern between ketamine and placebo, because of the short-term psychedelic effect of ketamine.[18] The Yale team published their results in 2000, but the medical community remained skeptical.[7] It was a small trial, after all, and the difficulties maintaining double-blind conditions made the conclusions, at best, only suggestive of an effect.[18]

Dennis Charney, MD, 2021 *(Photo by Claudia Paul)*

mountsinai.org/about/newsroom/2019/icahn-school-of-medicine-dean-dennis-charney-md-co-invented-a-patented-method-of-treating-patients-with-treatment-resistant-depression-which-is-part-of-the-drug-application-for-janssens-newly-approved-spravato-esketamine-ciii-nasal-spray

Replicating the Results

A few years later, Charney moved to the National Institutes of Health (NIH) and worked with a team headed by Carlos Zarate, Jr. They repeated the Yale study in 18 patients.[7,17] All of the patients had been diagnosed with treatment-resistant depression, having tried an average of six antidepressant drugs without finding relief. A few had also failed to respond to electroconvulsive therapy.[17]

In a randomized, double-blind, placebo-controlled crossover study, the patients were given a 40-minute intravenous infusion of a sub-anesthetic dose of ketamine (0.5 mg/kg). Within 2 hours, the patients in the ketamine group showed significant improvement in their depression, compared to the placebo group, and the effect remained significant throughout the following week.[17]

Both the rapid onset and the long-lasting effect from a single ketamine dose were breakthrough findings. All of the known antidepressant drugs (MAO inhibitors, tricyclic antidepressants, and SSRIs) take 6–8 weeks to achieve their full effect. In the 2006 publication of the NIH results, Zarate said, "To our knowledge, there has never been a report of any other drug or somatic treatment…that results in such a dramatic, rapid, and prolonged response with a single administration".[17]

It was an exciting finding. Ketamine was the first drug with a new mechanism of action to treat depression in more than half a century.[7]

Following the NIH report, other researchers confirmed Zarate and Charney's results.[7,11] Off-label use of intravenous ketamine for treatment-resistant depression became widespread. Patients who had gone through many antidepressant drugs (as well as talk therapy and even electroconvulsive therapy) without success were very willing to try other treatment options.[8,11,19] Ketamine often met that need.

Anesthesiologists and primary care physicians, along with some academic medical centers, accounted for most of the off-label use.[19] But increasingly, entrepreneurial practitioners set up freestanding specialty clinics to offer off-label ketamine (and perhaps other psychedelic drugs) to patients with depression.[12]

For some patients, ketamine was life-changing. Others did not respond.[7,12] There were no standard guidelines.[8] In most cases, intravenous ketamine seemed to relieve depressive symptoms after 1–3 treatments. In patients who experienced relief, subsequent sessions prolonged the antidepressant effect but did not produce any further dramatic relief of symptoms. Many practitioners offered eight treatments initially, and then the patient and doctor decided whether to taper or stop ketamine treatments, or to continue at longer dosing intervals.[8]

Proposed Mechanisms

The rapid antidepressant effect of ketamine has been attributed to antagonism of NMDA receptors. But this relationship is not completely understood, because other NMDA antagonists have failed to elicit the same robust effect.[7,11]

Ketamine is a non-competitive NMDA receptor antagonist and causes an increase in glutamate, the main excitatory neurotransmitter in the brain.[4,7,8,14,20] Specifically, ketamine binds to NMDA receptors on GABAergic inhibitory interneurons.[3,11] Inhibition of those interneurons leads to a sudden increase in glutamate, called the glutamate burst, which is apparently responsible for the rapid effect of ketamine on depression.[7,11,21]

The elimination half-life of ketamine is 3–4 hours, and for a long time, researchers were puzzled by the drug's extended clinical efficacy, which typically lasted for about 2 weeks after a single dose.[6,17,21] The explanation seems to be rapid restoration of disrupted synaptic connections in the brain.

irp.nih.gov/blog/post/2023/10/a-new-tool-in-the-battle-against-depression

Carlos Zarate, Jr., MD, at NIH Clinical Center

The glutamate system is very important in learning, memory, and other brain functions. In depression, glutamate synapses and circuits appear to be dysregulated.[11] Studies of chronic stress in rodent models, as well as clinical depression in patients, have revealed that neurons wither, and many synapses are lost.[13] Decreased synapse density has also been observed by electron microscopy in the prefrontal cortex of patients with depression.[13]

The burst of glutamate induced by ketamine stimulates downstream brain pathways, leading to protein synthesis and rapid increases in the number of synapses and spine density, particularly in the prefrontal cortex and hippocampus.[7,13,21] The repaired synapses and brain circuitry help to restore brain homeostasis.[11,13,15]

Researchers now think that the direct action on glutamate accounts for ketamine's rapid effect, whereas the older monoamine antidepressants act on these pathways more indirectly. And they think ketamine's glutamate-triggered restoration of brain synapses is key to its long-lasting antidepressant effect.[7]

The Downside

Although ketamine proved to be less hallucinogenic than PCP, psychoactive effects still limit its clinical use.[3]

A single sub-anesthetic intravenous dose commonly produces dissociation and both positive and negative psychotic-like effects. The dissociation effects include distortions in visual, auditory, or somatosensory stimuli, and

alterations in the perception of self or time. The positive psychotic-like effects include conceptual disorganization, hallucinations, suspiciousness, and unusual thought content. The negative psychotic-like effects include blunted affect, emotional withdrawal, and motor retardation.[17] These effects are dose-dependent and subside within 40 minutes after treatment termination. Repeated sub-anesthetic doses, over time, have been shown to lessen these effects.[17]

Ketamine's other side effects are also dose-dependent and self-resolving. Cardiopulmonary toxicity is rare and due to transient sympathetic-induced increases in heart rate and blood pressure.[3]

A Suspected Fatality

There is no known lethal dose of ketamine in humans.[4] Death from overdose is rare and usually involves other intoxicants or an accompanying trauma.[3,4] Ketamine's effects can be compounded when it is combined with other drugs that alter mood and perception, such as alcohol, opioids, benzodiazepines, and cannabis. Accidental deaths from falls, extreme hypothermia, and car crashes involving ketamine have also been reported.[4]

In October 2023, actor Matthew Perry was found floating face-down in his hot tub.[22] Later, the Los Angeles Police Department, Drug Enforcement Agency, and U.S. Postal Service opened an investigation into Perry's death, because the medical examiner found an anesthetic level of ketamine in his blood.[22]

Perry had been undergoing ketamine infusion therapy every other day but had recently reduced the dosing frequency. His last known infusion was 10 days before his death. Perry was also taking the opioid, buprenorphine, to treat his opioid use disorder. No other drugs or alcohol were in his system.[22]

There is no known lethal dose of ketamine in humans. Death from overdose is rare and usually involves other intoxicants or an accompanying trauma.

As complicating factors, Perry had diabetes, coronary artery disease, and chronic obstructive pulmonary disease. Until recently, he had been a two-pack-a-day cigarette smoker.[22]

Perry's high blood level of ketamine was puzzling, because ketamine (with its short half-life) should have cleared his system within hours after his last documented dose. Consequently, the focus of the officials' investigation was to determine the source (presumably illicit) of the ketamine in his system and how it got there. They were able to link several people to procurement of the drug.[22]

The high blood level of ketamine, although not fatal on its own, could have induced delusions and loss of motor control. In addition, ketamine's anesthetic effect could have been enhanced by Perry's opioid intake, poor pulmonary function, and cardiovascular disease, leading to accidental drowning.[22]

On August 15, 2024, five people, including Perry's live-in assistant, were charged with selling or administering the ketamine that led to his death.

Moving the Needle

The robust and now widely acknowledged antidepressant efficacy of ketamine prompted more formal acceptance—and regulation—of its use in treatment-resistant depression.

In 2017, an American Psychiatric Association task force said there was "compelling evidence" to support the antidepressant effects of ketamine infusion, despite gaps in the clinic al data.[11] The task force's chief concerns were ketamine's long-term safety and durability, which had not yet been adequately studied. That data would be needed to properly guide its use.

Ketamine is a racemic mixture of the S(+) isomer, known as esketamine, and the R(-) isomer, known as arketamine. Esketamine has 3- to 4-fold higher binding affinity to NMDA receptors than arketamine.[14] It is about 3-times more potent for anesthesia and analgesia than arketamine.[4,11] Esketamine is also associated with less cardiac stimulation, less spontaneous motor activity, fewer psychotic-like side effects, lower incidence of emergence delirium, and more rapid recovery than arketamine.[3]

Making it Official

In 2016, researchers at Janssen Pharmaceuticals published a report of esketamine's effect on treatment-resistant depression.[14] Thirty patients were given a slow intravenous infusion of sub-anesthetic doses of esketamine in a randomized, double-blind, placebo-controlled study. Like ketamine, esketamine produced a rapid, robust, and persistent improvement in the patients' depressive symptoms after a single dose.[14]

This was the first study to profile esketamine in treatment-resistant depression, and the isomer's efficacy was both statistically significant and clinically meaningful.[14]

Janssen decided to move forward with development of a commercial esketamine product in the form of a nasal spray. The nasal spray would be absorbed about as rapidly as intravenous infusion but would be easier for doctors and patients to administer.[7] Because of the anticipated clinical advantages of esketamine compared to conventional antidepressant drugs, the FDA designated the compound as a Breakthrough Therapy, which facilitated its rapid clinical development.[15]

In randomized double-blind clinical trials (TRANSFORM), patients with treatment-resistant depression were given an oral antidepressant drug, along with either esketamine or placebo.[15,16] The benefits of esketamine were apparent within 1 day, and the effect remained statistically significant for 28 days.[15]

This was the first time that an antidepressant (esketamine) was shown to be superior to an active comparator (an oral antidepressant drug) in any clinical trial of major depressive disorder.[15]

In follow-up studies (SUSTAIN), continued treatment of the patients with twice-a-week dosing for 18 months showed that relapse of depressive symptoms was significantly less likely to occur in the esketamine-treated group than those receiving placebo.[16]

On March 5, 2019, the FDA approved esketamine nasal spray (Spravato®) for use in combination with an oral antidepressant for treatment-resistant depression.[23] Janssen's product was the first FDA-approved esketamine for any use. However, because of the risk of sedation and "dissociative" effects, and the potential for abuse and misuse, Spravato was classified as a Schedule III controlled substance, and its use was further restricted by a Risk Evaluation and Mitigation Strategy (REMS) program.[23]

Under REMS, pharmacies and healthcare personnel who purchase, dispense, and/or supervise administration of esketamine must be FDA-certified.[16,23] Only patients enrolled in the REMS program may receive the drug, and they must be monitored during and for at least two hours after drug administration. Esketamine cannot be dispensed directly to the patient for at-home use.[16,23]

Addressing Suicide, Finally

Depressed patients with suicidal ideation show more severe symptoms and respond less well to treatment, compared to those without suicidal thoughts.[24] In fact, clinical trials of antidepressant drugs have excluded patients exhibiting suicidal behavior, because such patients were considered the least likely to respond.[24–26]

The prevalence of suicidal ideation in major depressive disorder is as high as 60%, and the lifetime incidence of attempted suicide in this population is 10–20%.[24,26] These patients constitute a psychiatric emergency, and until recently, there were no approved emergency medications. The standard of care included initiation or optimization of oral antidepressants, and frequently, patients were hospitalized to prevent self-harm. The benefits of hospitalization were short-lived, and the risk of attempted and completed suicide remained high in the weeks immediately following discharge.[24,26]

The time between onset of suicidal thoughts and suicide attempt is often very short, highlighting the need for immediate intervention.[8,17,26] Unfortunately, the 6- to 8-week lag in onset of conventional antidepressant drugs limits their utility in these crisis situations.

Because of ketamine's fast-acting antidepressant effect, it was reasonable to suppose that it might also benefit those at high risk of suicidal behavior. In addition to esketamine's demonstrated efficacy in treatment-resistant depression, Janssen's clinical trials provided evidence that esketamine might also decrease suicidal thinking.[16,26]

Again, the FDA designated esketamine nasal spray as a Breakthrough Therapy for major depressive disorder with imminent risk for suicide. That facilitated the drug's development for this new indication.[15]

Janssen's clinical trials (ASPIRE I and ASPIRE II) marked a major milestone in investigations of antidepressant drugs. Esketamine nasal spray (Spravato), in combination with an oral antidepressant, reduced the severity of patients' suicidality within 24 hours.[24–26] The benefit was greater in the esketamine plus oral antidepressant group than those receiving only a standard-of-care antidepressant, and the esketamine effect lasted up to four weeks.[24–26]

Spravato® (esketamine nasal spray)

On August 3, 2020, the FDA approved esketamine nasal spray for treatment of patients with major depressive disorder and acute suicidal ideation or behavior.[25] It was the first drug approved for this indication and may fulfill the unmet need for a rapidly acting drug in this patient population.[24,25]

Off-label Popularity

Since the approval of ketamine in 1970, physicians have been legally permitted to prescribe it for any medical condition. Consequently, after the discovery in the early 2000s that sub-anesthetic doses rapidly diminished the symptoms of major depression, practitioners began administering it off-label.[3,10]

Although many of these healthcare providers carefully screen their patients and diligently monitor them during and after treatment to manage any hallucinatory side effects, the entrepreneurial practitioners at specialty/standalone clinics do not comply with the strict regulatory requirements imposed on Spravato. Clinics, like the one where Lila received her

prnewswire.com/news-releases/janssen-announces-us-fda-approval-of-spravato-esketamine-ciii-nasal-spray-for-adults-with-treatment-resistant-depression-trd-who-have-cycled-through-multiple-treatments-without-relief-300807366.html

treatment, administer ketamine (the racemate) by intramuscular injection, not esketamine by nasal spray. And they do not administer ketamine in combination with an optimized regimen of an oral antidepressant, which is required for Spravato administration.

In addition, they do not follow the procedures for drug storage, accountability, and reporting that are required by REMS for Spravato. This is especially concerning, because there is little data on the effects of long-term, low-dose administration of ketamine/esketamine.[16,25] Similarly, controlled clinical trials of ketamine's abuse potential are lacking.[4]

Hints of Concern

Long-term studies are needed both to determine the durability of the antidepressant effect and to establish the safety of long-term exposure.[4,7,8,19] Toxicology testing in animals suggests that long-term administration may cause long-lasting changes in brain neuronal circuitry and perhaps irreversible changes in behavior.[4]

Despite the lack of controlled trials, the effects of chronic exposure have been derived from recreational use.[4] In a one-year observational study of recreational users, frequent use (more than four-times per week) was associated with impaired short-term and long-term memory.[14] But those memory-related deficits have been difficult to link directly to ketamine, because of complicating comorbid and environmental factors.[4]

Long-term use may also lead to flashbacks, attentional dysfunction, and decreased sociability. There may also be pronounced and persistent neuropsychiatric effects, including schizophrenia-like symptoms, cognitive impairment, and poor psychological well-being.[3,4]

Despite its abuse potential, instances of ketamine dependence are relatively rare, although some isolated cases have been reported. There is also evidence suggesting that repeated ketamine use may lead to drug tolerance.[4]

More to Come

The antidepressant efficacy of ketamine has inspired researchers to explore it for other mental and emotional disorders.[3,7,10,11] Clinicaltrials.gov lists dozens of clinical trials investigating ketamine for PTSD, obsessive-compulsive disorder, bipolar disorder, and anxiety, among others. Researchers are also conducting structure-activity studies to try to maximize ketamine's antidepressant efficacy and minimize its psychotic-like properties.

Ketamine's impressive track record has also sparked interest in other psychedelic drugs including psilocybin, LSD, ayahuasca, and MDMA (ecstasy). Those compounds are also being studied for treatment of depression, PTSD, obsessive-compulsive disorder, bipolar disorder, and anxiety.[3,7,11,20] But that's another story.

References can be found on page 36.

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