THE SCIENTIST BATTLING THE ADDICTION CRISIS

Nora Volkow leads the world's biggest funder of addiction research, and now she's facing her greatest test in the opioid crisis. **By Emiliano Rodríguez Mega**

On a cold Friday night in February 1995, addiction researcher Nora Volkow and her husband got into their car after a long day at Brookhaven National Laboratory in Upton, New York. Ice had covered the trees and the roads, making them sparkle. But as the couple drove down a slope, the tyres lost their grip. The vehicle spun out of control. Volkow curled up to shield herself as an oncoming car crashed into her door.

Metal bit into her flesh. The pain was unrelenting. Finally, the fire service arrived to break her free and an ambulance rushed her to the nearest emergency department, where a doctor gave her Demerol, a powerful and highly addictive opioid painkiller also known as pethidine, which is similar to morphine.

Volkow had spent countless hours talking to people with addiction and had read hundreds of papers on the mechanisms of drug abuse. Neither prepared her for what happened next.

"It was extraordinary, those impressive sensations," she says. A moment of ecstasy, one she describes as comparable only to long-lasting sexual pleasure, eclipsed all other feelings. She stayed on the medication for another few days and was sent home with more. But she decided not to take it. She was afraid — she knew many of her patients could not stop once they started. She would get through the pain without the help of drugs.

That night, a discomfort she had never felt before overran her body. She felt restless, agitated, desperate. Volkow took a painkiller and, like an apparition, the feeling faded away. "It was then that I realized how fast dependence develops," she says. "It also made me realize that I'm very afraid of opiates."

Twenty-five years later, Volkow's name has become widely known in the addiction field and beyond. As a neuroscientist who has directed the US National Institute on Drug Abuse (NIDA) in Rockville, Maryland, since 2003, she has championed the idea of addiction as a disease of the brain rather than a moral failing. Under her direction, NIDA has prioritized research on the biological basis of addiction, and fought against the mistreatment of drug abusers in both the medical and criminal-justice systems.

Her quest has taken on a new urgency as the United States finds itself contending with shifts in the legal status of cannabis, a growing market for electronic cigarettes, a sudden comeback of cocaine and methamphetamine, and a two-decade-old opioid epidemic that has devastated many parts of the country: opioid overdoses have killed nearly half a million people in the United States (see 'Tackling the opioid epidemic'). In response, her agency has started projects to monitor drug use and has ploughed money into medications that can reduce the cravings and pleasurable effects of drugs.

Critics have long argued that Volkow's emphasis on the brain minimizes the roles that social and economic forces have in making people prone to addiction. In the past year, Volkow has begun to acknowledge that factors such as homelessness, unemployment and isolation can make people more vulnerable to drugs and less likely to recover. But some researchers contend that the agency's funding decisions have been slow to reflect this shift in mindset. They say that NIDA's focus on the brain is disproportionate, and they worry about its outsized power over policies tackling drug use and addiction. "NIDA's influence is significant; people follow that lead," says Ingrid Walker, a cultural-studies researcher at the University of Washington in Tacoma.

Nonetheless, Volkow's obsession with

Nora Volkow at her childhood home in Mexico City.

ALEJANDRA RAJAL FOR *NATURE*

understanding the biological effects of excessive drug use – fuelled in part by her own family's past – has not only shattered dogmas in neuroscience; it has also helped to mitigate the stigma faced by those living with addiction.

"Her mission in life was to harvest the power of science to change lives of millions of people," says Bertha Madras, a psychobiologist at Harvard Medical School who is based at McLean Hospital in Belmont, Massachusetts. "And she has done that."

Revolutionary heritage

Volkow grew up in Mexico City, one of four daughters of Soviet and Spanish immigrants. Their mother, an haute-couture dressmaker from Madrid, sought refuge in Mexico to escape Francisco Franco's dictatorship. Their father, a chemist, was also a refugee. He had come to Mexico City as a 13-year-old in 1939 to live with his only surviving relative – his grandfather, the exiled Soviet revolutionary leader Leon Trotsky.

As a teenager, Volkow was captivated by the human brain and studied medicine at the National Autonomous University of Mexico in Mexico City. Her father encouraged her without limits. "Whatever I asked my dad that had to do with science, the answer was 'yes'," she says. She once asked him if she could bring home a corpse and dissect it. He approved; Volkow's mother and sisters threatened to leave the house. But she did end up with some bones to examine. "When something interests me," she says, "I won't quit until I understand it."

That same curiosity and stubbornness would guide most of her career. After graduating top of her class, she was accepted to study psychology at the Massachusetts Institute of Technology in Cambridge. But a 1980 article in *Scientific American* disrupted her plans.

The piece described how a new technology, positron emission tomography (PET), was allowing neuroimagers to look into living brains and watch their activity patterns. Volkow was instantly hooked.

Soon after reading the article, she secured a research job in the lab of psychiatrist Jonathan Brodie at what was then New York University (NYU) Medical Center in New York City, which had a vibrant programme using the technology for neuroimaging. Brodie was starting to do PET scans with the aim of studying various brain disorders in people.

"Clearly, she was a star from the beginning," says Brodie. "Her enthusiasm was boundless." Volkow soon became involved in every project, from looking for brain-tumour biomarkers[1] to detecting differences in brain activity between people with and without schizophrenia[2]. Her reputation as a rebellious yet brilliant scientist began to take shape. "Nora was certain that she was always right, and sometimes she was," says Brodie. "Perhaps, even, most of the time."

Scanning for insights

By the mid-1980s, Volkow had completed a psychiatry residency at NYU and moved to the University of Texas Health Science Center in Houston to work in its imaging facility. She intended to study schizophrenia, but the cocaine craze was bringing with it a surge of addicted people.

In PET scan after PET scan, Volkow spotted anomalies in these individuals' brains. "You'd see holes, gaps where blood flow should be," she says. She suggested that cocaine chokes blood vessels to the extent that they don't allow proper circulation[3] – similar to small strokes. Her findings contradicted the belief, common at the time, that cocaine was a relatively safe substance – although the 1986 deaths of two celebrated US sportsmen (basketball player Len Bias and American football player Don Rogers) changed that perception.

In 1987, Volkow moved to Brookhaven National Laboratory, where for the next 16 years she continued to probe the effects of drugs on the brain. She used radioisotopes to label cocaine, tracking how rapidly it triggers the neurotransmitter dopamine in the brain and how quickly it dissipates, and arguing that the speed of its effect could explain why the drug is so powerfully addictive.

While at Brookhaven, Volkow kept questioning long-held assumptions in neuroscience. The general agreement was that addictive substances impaired the brain's reward centres, tempting people to keep trying the substances to feel good. But that didn't explain why so many patients had told her that they felt compelled to take the drugs, even when they had long lost that pleasure. It was as if they had lost the power to decide. This more-complex reaction seemed to implicate more than just the brain areas that process reward.

A series of key discoveries came in the 1990s. Volkow noticed that the prefrontal cortex, the brain region that regulates decision-making and self-control, was underactive in men who were addicted to cocaine – an anomaly that might sometimes precede addiction, making a person more vulnerable to it. Dysfunction in decision-making regions, she suggested, was why drug-addicted people felt they had lost control. Furthermore, she and her team found, repeated cocaine use desensitized the brain by killing off dopamine receptors, which diminished the reward people felt from the drug even as it increased their dependence on

it[4]. Volkow and her colleagues later replicated these results in people who had misused alcohol, heroin or methamphetamine.

The blobby PET images were diagnostic enough for Volkow to identify which belonged to addicted people and which didn't. "It put a totally different picture on it," says radiochemist Joanna Fowler, one of Volkow's closest collaborators and friends at Brookhaven who retired in 2014. "Going from that perception of addiction as a moral weakness or a lack of willpower to that of a brain disease."

Volkow added more discoveries: she found that some brain changes wrought by alcohol addiction can be reversed after months of abstinence[5], for example, and that dopamine influences people's motivation[6], a process that is dysregulated in drug addiction.

Her ideas went against convention, says psychologist Alan Leshner, former chief executive of the American Association for the Advancement of Science in Washington DC and Volkow's predecessor at NIDA. Implicating decision-making brain regions went against decades of work. "I know that people thought she was weird."

If Volkow knew, she didn't care. "She was an extremely courageous scientist" who broke open an entirely new approach to looking at the brain, says Leshner. In 2003, Volkow took over as director of NIDA, now a US$1.3-billion-budget agency that funds more scientific research on addiction than any other in the world.

Volkow is the longest-standing director in NIDA's history. During her tenure, she has continued her own investigations, amassing evidence on the basic biology of drug abuse, and her agency has supported many others.

NIDA has funded studies showing how marijuana can be addictive, especially for young or regular consumers, for example, and has supported research into the role of genetic and epigenetic factors related to addiction.

The agency has also lent its support to the treatment and prevention of drug misuse. It helped to develop the first US-approved medication (lofexidine) that alleviates physical symptoms of opioid withdrawal, and funded early trials of long-acting implants under the skin that are now used in patients to ease opioid withdrawal over months.

Furthermore, NIDA funds research to develop technologies aimed at helping people who are addicted — including an app that connects them with coaches and with others in recovery, and a tool that uses data science to find prescription painkillers being sold online illegally.

Some of that work fits in with other efforts that have led to positive trends in the opioid crisis. For the first time since 1990, for instance, drug-overdose deaths in the United States dropped by around 5% in 2018.

Volkow has questioned the standards for approving addiction medication set by the Food and Drug Administration (FDA): until it changed its policy in 2018, the FDA had approved such treatments only if they could show that they fostered abstinence[7]. And Volkow alleges (although some critics disagree) that reframing addiction as a pathological condition contributed, at least in part, to legislation such as the US Mental Health Parity and Addiction Equity Act of 2008, which requires insurance companies to put substance-use disorders on an equal footing with other diseases.

"I think that the United States and the world is very fortunate that Nora accepted the job as NIDA director," says Madras.

In the family

A headstone engraved with a hammer and sickle guards the ashes of Volkow's great-grandfather in the garden of her childhood home, in a cobblestoned neighbourhood in Mexico City. In 1940, long before Volkow was born, Trotsky was killed in the house by a Stalinist agent bearing an ice axe. The house is a monument to Trotsky's attempts to evade harm: bricked-up windows, armoured doors and three watchtowers.

It is the day after Christmas, and tourists drift around the house — now a museum — absorbing the history of Volkow's family. Volkow has come back to Mexico City to visit relatives, as she does almost every year. She stares at the little metal door in the headstone that contains her great-grandfather's urn and stays quiet for a moment.

"It was kind of shocking, having death so close, almost tangible," she finally murmurs. "No one grows up having someone buried in their garden."

Trotsky, one of the leaders of the October Revolution of 1917 that ultimately led to the creation of the Soviet Union, dreamt of establishing a mass upheaval worldwide that would give power to the most vulnerable and foster equality.

Similar ideals live on in Volkow. During her career, she has often felt that the US medical and criminal systems discriminate against addicted people by ignoring their drug misuse, denying them medical attention and locking them up. That "opened my eyes to the opportunity to use evidence to change these practices" and provide a scientific way to explain and treat addiction, she says.

But she also has a more personal motivation — addiction ran deep on her mother's side of the family. As a child, Volkow remembers huge secrecy surrounding her uncle Rafael, a handsome and kind man who struggled with alcohol misuse. And it wasn't until her mother was dying, decades later, that she told Volkow that her grandfather had not died of heart complications, as everyone was told; not able to control his alcoholism, he had killed himself. The confession was heart-breaking. Volkow had devoted her entire academic life to showing how addiction was a disease like any other, not a shameful condition.

"That is what stigma does," she says. "My poor mom had to wait until the last moment to tell me something she didn't dare to."

The stigma of addiction is still powerful. It could explain why only 17% of the 21.2 million people in the United States diagnosed with substance-use disorders in 2018 received treatment. Yet Volkow's message has not been entirely lost. She has helped to reframe addiction in society, giving public talks, educating local and federal judges, providing training tools for physicians and pushing to make overdose-reversing and anti-craving medications more available in rehabilitation facilities and prisons.

Brain bias

But a substantial number of researchers disapprove of how NIDA conceptualizes addiction as a disease of the brain, an approach that Volkow has strengthened during her tenure. They claim that the science behind the agency's vision is valuable, but incomplete; that its focus on neuroscience skews research on drug misuse by neglecting economic and social-scientific approaches to curtailing addiction; that it

> "THE WORLD IS VERY FORTUNATE THAT NORA ACCEPTED THE JOB AS NIDA DIRECTOR."

A young Nora Volkow in the late 1970s.

ESTEBAN VOLKOV

hasn't delivered many new medications; and that it implicitly, and perhaps unconsciously, perpetuates the war on drugs.

In 2009, Wayne Hall, an addiction epidemiologist at the University of Queensland in Brisbane, Australia, began to scrutinize the neuroimaging evidence of addiction. By the end of the project, "I came to the view that the science wasn't as clear as it's often presented", he says.

He and his colleagues found that most of the studies, including Volkow's, used small samples of people who were severely addicted, and did not tease out which brain differences they might have had beforehand[8]. The data did not seem strong enough to justify the emphasis on the brain as an explanation for addiction. "If you focus on what goes on between the ears," Hall says, "you often tend to neglect broader social policies that we know can have a big impact on the prevalence of drug problems."

Others echo that criticism. NIDA's overemphasis on neurobiology has extracted drug misuse from its societal and economic context, such as poverty and racism, and disregarded other models that see addiction as something people can unlearn[9], says Derek Heim, an addiction psychologist at Edge Hill University in Ormskirk, UK. "It's more than just brains having gone wrong."

Some also argue that the political attention the agency gets could translate into harmful policies. Spreading the message that drugs cause a brain disease often results in draconian measures aimed at controlling drug supply at all costs, says David Courtwright, a drug historian at the University of North Florida in Jacksonville. "I think that sometimes makes Nora and others at NIDA feel uncomfortable because they really don't want to see addicts sent to jail – they want them to be treated," he says.

But even among her detractors, Volkow has unexpected support. "I really admire her," says Courtwright. "I think she's been a very effective leader for NIDA." And they recognize important improvements.

Last year, for example, Volkow launched a project that will follow almost 11,900 healthy children into early adulthood, using neuroimaging to capture how a child's biology and social environment – including any substance use – affect their brain development. This could help to clarify which brain anomalies precede addiction and which might cause it. The results will be complemented by another study, currently being planned, that will evaluate the long-term impact of prenatal and postnatal drug exposure on the brain.

NIDA is also spearheading a project that aims to reduce opioid-related deaths in badly affected regions. The $354-million effort, launched last year, aims to cut deaths by 40% by 2023 in 67 communities in the states of Ohio, New York, Massachusetts and Kentucky. Researchers will test strategies that can reduce opioid-prescription rates, that increase the number of people receiving medication-assisted treatment and that expand the distribution of naloxone – an antidote that is sprayed into the nose or injected to try to save those who have overdosed.

On a hot day in October 2019, Volkow visited Kensington, a neighbourhood in Philadelphia, Pennsylvania, where the US drug crisis has left a deadly trail. Syringes littered the streets. People injected themselves in broad daylight and others lay on the ground, showing clear symptoms of withdrawal. An emaciated man shared a piece of glazed doughnut with a shivering friend.

The scene shocked her. She had decades of experience studying drug addiction in the lab and funding the research of others, and it was not enough. "This is real," she thought. She realized that if she didn't address the social realities of drug addiction, she wouldn't solve the epidemic or prevent future ones.

Months have passed since Volkow's trip to Kensington, but a thought has swung back and forth in her head like a pendulum ever since. If people don't have a place to sleep or food to eat, they won't have a fighting chance of breaking out of their addiction – no matter how many medications NIDA funds or how many brains she scans.

During her December visit to the Trotsky museum, her old house, Volkow goes to the quiet library, away from the crowd. Memories of her uncle and grandfather begin to resonate, and the scenes she saw in Philadelphia fill her thoughts.

She knows now that there is a lot more to their struggles with addiction than a damaged brain.

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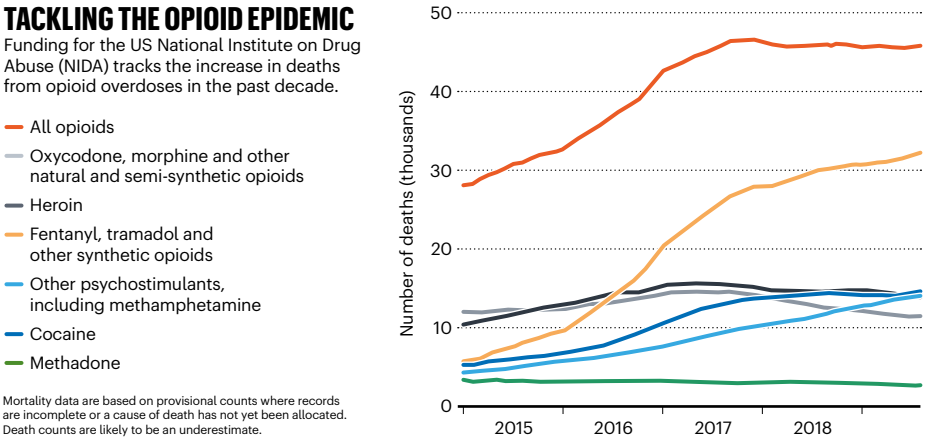
TACKLING THE OPIOID EPIDEMIC

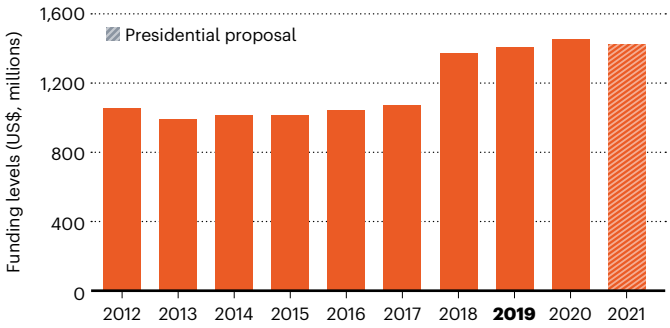
Funding for the US National Institute on Drug Abuse (NIDA) tracks the increase in deaths from opioid overdoses in the past decade.

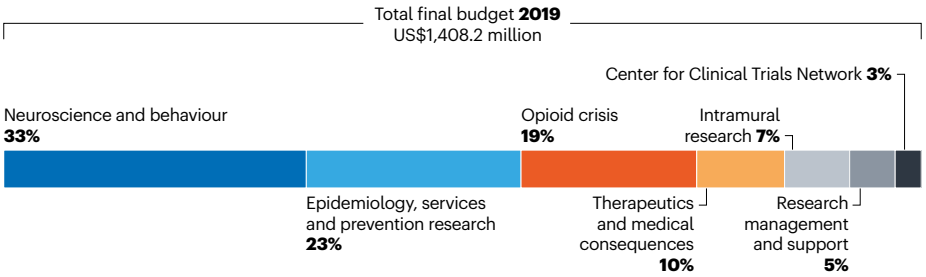


Mortality data are based on provisional counts where records are incomplete or a cause of death has not yet been allocated. Death counts are likely to be an underestimate.

Funding

NIDA's budget jumped in 2018, and the agency has since targeted funding specifically to the opioid crisis. It has boosted the amount of support for research into the social and economic conditions that foster drug misuse, and continues to fund more neuroscience projects than any other type of addiction research.





SOURCES: DEATH COUNTS: F. B. AHMAD *ET AL.*/US NATL CENTER FOR HEALTH STATISTICS; BUDGET AND ACTIVITY: NIDA.