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Democracy Dies in Darkness

Ultrasound technology is used in many ways. Addiction is the next frontier.

The use of the high-frequency sound waves is also being adapted to treat Alzheimer's disease, tumors and psychiatric disorders.

By David Ovalle

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MORGANTOWN, W.Va. — Nestled inside a giant MRI machine, the woman wears a helmet outfitted with special probes. Peering through high-tech goggles, she sees images designed to trigger the awful, familiar cravings that have wrecked her life.

Heroin residue on tin foil. Lines of powder cocaine. Pain pills scattered on a table.

At the same time, scientists buzz around a small observation room, scrutinizing brain scans on computer monitors, calibrating measurements, tweaking data points. Beams of ultrasound waves fire into a tiny sector of the woman's brain by the hundreds — an experimental treatment that researchers hope will essentially reset her mind and ease her cravings for drugs.

The April clinical trial session at West Virginia University's Rockefeller Neuroscience Institute opens a window into a growing school of research that repurposes a tried-and-true scientific tool, ultrasound, in a more focused fashion. The use of the high-frequency sound waves is being adapted to treat Alzheimer's disease, tumors and psychiatric disorders. Now, researchers are studying whether ultrasound can be deployed against an especially implacable foe: addiction to opioids and other substances.

"It's basically doing brain surgery without the surgery," said Ali R. Rezai, director of the Rockefeller Neuroscience Institute.

Researchers are finishing the initial phase of the clinical trial, funded largely by the National Institute on Drug Abuse. In May, they hope to start the next phase, which will include patients who receive the ultrasound treatment and, crucially, participants exposed only to placebo sound waves, to better gauge the effects of the treatment.

Scientists caution that research into focused ultrasound — including for ailments of the mind, such as substance use disorder — remains in its infancy. They warn that the treatment for addiction is not a cure-all and would be used alongside other therapies. Even if the technology pans out, it could be years before the Food and Drug Administration approves ultrasound for treating addiction.

The challenges were underscored during the session for the 20-year-old woman, who is battling a fentanyl addiction

that fueled multiple overdoses and who was not identified by researchers because of privacy concerns. It was not as simple as flicking a switch. The software, ultrasound machine and MRI used to guide the waves were not designed for this use. So researchers adjusted settings, revving up the system like an old car to reach sufficient wattage.

Amid the hum of the machine and beeps of heart monitors, Rezai analyzed readings alongside team members.

"We're not getting enough dose in her," Rezai told them.

They zapped her in blocks of five minutes. After each, the woman used handheld controllers to rate drug cravings on a zero to 10 scale, a rough but real-time estimate of the ultrasound's impact. Her answers flicked on the screen. At one point early on, her desire to use heroin stood at 6.5. For pills, the reading was 9.

They've got the power

For decades, researchers aiming to treat neurological and psychiatric conditions have harnessed energy to stimulate the brain. Several methods are used with mixed success.

The oldest, electroconvulsive therapy — ECT — treats major depression, schizophrenia and bipolar disorder by sending electrical currents through the brain, prompting seizures. Another treatment, transcranial magnetic stimulation, or TMS, employs magnetic pulses to stimulate nerve cells in the brain.

With deep brain stimulation, or DBS, surgeons implant a neurostimulator that delivers electrical pulses into the brain. It is approved to treat conditions including essential tremors, Parkinson's disease and obsessive-compulsive disorder.

During one highly touted study involving deep brain stimulation, researchers at the Rockefeller institute implanted stimulators into a handful of opioid-addicted patients. The results seemed promising, but the center has pivoted away from that research because major invasive brain surgery is risky and because focused ultrasound may prove safer and more affordable, Rezai said.

In all, the FDA has greenlit focused ultrasound to treat nine conditions, including essential tremor and noncancerous uterine growths. Regulators have approved it for 32 uses worldwide, according to the Focused Ultrasound Foundation, which facilitates and funds research.

Focused ultrasound is being researched and developed for more than 180 uses, said Neal F. Kassell, the group's founder and chairman and a former neurosurgery co-chair at the University of Virginia. "Ten years ago, there were only three" uses being researched, he said. "That gives you an idea of how rapidly the field is growing."

At higher intensity, the beams burn away tissue. At low intensity, they can stimulate or restore abnormally functioning tissue. The Rockefeller institute is also involved in trials using low-intensity ultrasound to help the brain better absorb Alzheimer's medications.

Some 2,000 miles away from West Virginia, researchers are also using low-intensity ultrasound but without the giant MRI.

At the University of Utah, researchers invented a headphones-style device that delivers the same low-intensity waves without using an MRI. They are testing it on patients to treat major depressive disorder and expect to soon start trials involving food addiction, opioid use disorder, post-traumatic stress disorder and Alzheimer's.

The device, dubbed DIADEM, will be more affordable than using "completely impractical" and expensive MRI machines to guide the sound waves, said Jan Kubanek, a Utah neuroscientist helping lead the research who believes the approach has the potential to be used at a large scale.

Participants do not have to shave their heads as they do with MRI procedures, which is done to help the sound waves better penetrate the skull, Kubanek said.

At U-Va., scientists have treated six patients with ultrasound and reported no harmful side effects, said Nassima Ait-Daoud Tiouririne, director of the university's Center for Leading Edge Addiction Research. Unlike the opioid study in neighboring West Virginia, the U-Va. center is targeting users who prefer cocaine. "There is no medication for cocaine," she said. "It's really hard to treat."

The researchers focus on a part of the brain known as the insular cortex, which is believed to play a key role in heightening the sensation of drugs. Researchers at the Neuromodulation Clinic at the Washington VA Medical Center in D.C. are studying how focused ultrasound also affects that area of the brain in veterans addicted to nicotine.

By contrast, the West Virginia researchers target the nucleus accumbens, part of the brain's reward circuitry. Researchers say repeated drug use can electrically and chemically alter the nucleus accumbens.

It remains unclear what the sound waves are doing inside the brain. Rezai suspects the vibrations alter the membrane of the nucleus accumbens, changing the functioning of cells and essentially resetting the brain. Whatever the mechanism, he said, bursts of the sound waves over 15 to 20 minutes show rapid reductions in cravings.

Rezai said patients have not reported adverse effects from the procedure.

The hot zone

The story of a 29-year-old mother, who spoke on the condition of anonymity because of the sensitivity of her condition, is achingly familiar in West Virginia, a hot zone of the opioid crisis ignited by prescription pain pills flooding the state.

As a teen, she took opioid pills recreationally with friends, then cocaine, along with other substances. In her 20s, she moved on to heroin and fentanyl pressed to look like pain pills. While still grappling with drugs, she gave birth to a baby, lost custody of the boy to social services and wound up in rehab, where she was offered a slot in the ultrasound

study.

“I’m willing to do anything. I want my family back,” she said of the decision to volunteer. “I don’t want to use anymore. I just want to be happy and healthy and be a good mom and be a good person.”

Like all study participants, she was stable and on medication — in her case, buprenorphine — designed to reduce cravings and stave off withdrawal symptoms. Researchers acknowledge it can be difficult to disentangle the separate effects of the medications and the sound waves.

But for patients on medications alone, photo prompts of drug use still activate cravings, said James Mahoney, a clinical neuropsychologist at West Virginia University working on the research.

The mother recalled seeing photos in the study that showed baggies of fentanyl and people smoking heroin. “I would get this feeling throughout my body, like I was about to jump out of my skin because I wanted to do it so bad,” she said.

During the roughly two-hour session in the MRI machine, she said, she wasn’t sure when the ultrasound was administered. But toward the end, her body suddenly “felt warm and fuzzy, and I felt like calm.”

In the hours and days afterward, she said, the pictures no longer triggered her. She worried the cravings would return. More than eight months later, she said, they have not. Her crippling anxiety has dissipated. She is living with her boyfriend and has reunited with her toddler son.

For Patient 19, the woman who underwent the procedure in April, the results didn’t seem as clear-cut at first.

Pierre D’Haese, director of imaging analytics, peered at a 3D model known as tractography, which shows bundles of neon pink, green and purple strands inside her head depicting neural highways connecting parts of the brain. The model helped them target the nucleus accumbens buried nine centimeters deep into the skull. Precision was imperative: A tad in the wrong direction might trigger activity on the highway that regulates anxiety, he said.

“We’re trying to fine-tune one millimeter at the same time,” D’Haese said.

Inside the control room, Rezai and his team — including engineers from the ultrasound machine manufacturer Insightec monitoring remotely from Israel — activated the device during a series of five-minute sessions. Images of drug use flashed in the woman’s goggles. Sixty watts. Seventy. Eighty. The waves weren’t maintaining a high enough wattage. During the final session, they adjusted the target in the brain slightly. The pulses reached more than 90 watts consistently.

The team breathed easier. Results fared better. From inside the MRI machine, the woman indicated her craving for heroin had dropped to just 3, pills to 6.

It’s not unusual for patients to report the greatest effect days later. Researchers will pepper the woman with questions, and scan her brain, for days, weeks and months. On this day, the woman emerged from the MRI smiling — something Mahoney, the neuropsychologist, hadn’t seen in their earlier meetings.

"After the procedure, she was definitely much, much brighter," he said.