In monkey trial, gene therapy shows promise in curbing severe problem drinking

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For people with severe alcohol use disorder, a new gene therapy trial

could lead to an effective treatment that would involve chemically rebalancing the area of the brain associated with addiction.

"With alcohol alone, there's generally more than 100,000 deaths [in the United States] per year," said Dr. Tucker Woods, associate medical director of Lenox Health Greenwich Village in New York City, who was not part of the study. "And just think about the impacts on families when somebody's addicted. The impact is not just to that patient, it's also their family and friends. So if this pans out in humans, it could potentially be a game changer, if they could fix that hijacked pleasure/reward pathway of the brain."

For the research, a team at Oregon Health & Science University (OHSU), in Portland, tested a form of gene therapy used to treat Parkinson's disease, with the goal of resetting the dopamine reward pathways in monkeys after they voluntarily and heavily drank alcohol.

The scientists inserted a gene called glial-derived neurotrophic factor (GDNF) into the region of the brain where dopamine exists in four of the monkeys, via a type of brain surgery called a craniotomy. GDNF stimulates cell growth, and the scientists discovered the gene effectively reset the monkeys' brain reward pathways. Compared to the control group, the consumption of alcohol in the monkeys that underwent the procedure dropped by more than 90%.

"A big problem in treating alcohol use disorder is the return to drinking after abstinence is achieved. So that's really what we wanted to address," said senior study co-author Dr. Kathleen Grant, a professor and chief of the division of neuroscience at OHSU's Oregon National Primate Research Center.

"It's the first demonstration in monkeys that this constitutively active increase in dopamine can, in fact, lower drinking levels down to near

zero," she explained. "So, we're concluding that this is probably a really viable target."

Grant noted that this treatment option would be for especially serious cases of alcohol addiction.

"This is an irreversible treatment. So, it would only be appropriate in the most severe cases that have already shown that other therapeutic approaches are not effective in the chronic drinker," she explained.

The study was published Aug. 14 in the journal *Nature Medicine*.

Alcohol-related deaths are the fourth-leading preventable cause of death in the United States, one study showed. And drinking has been on the rise; the average American is having over 500 standard drinks in a year, or about 2.5 gallons' worth, according to the U.S. National Institute on Alcohol Abuse and Alcoholism.

The health costs are myriad: the U.S. Centers for Disease Control and Prevention cites serious heart, liver, blood and digestive problems, an increased risk of several types of cancer, a weakening of the immune system, learning and memory problems, mental health problems, social problems and dependency issues.

Woods said it's important to remember the science behind why addiction occurs.

"Up until 1980 or so, people thought that addiction was essentially a moral failure, and then somewhere I would say around 1980 or so, medicine came around and said, 'Not so fast.' Medicine said that addictions very much are chronic relapsing illnesses like diabetes, high blood pressure, schizophrenia, depression and all of these other disorders," he said.

"And the true cause of addiction are these biological, psychological and social forces. And when these forces come together, they change something in the brain, if you will. They flip the brain switch on. And then once there's been these changes to the brain, at that point, the addiction has a life of its own, independent of the forces that set it into motion to begin with," Woods added.

Grant is hopeful that, after more rounds of testing, her team's study will eventually lead to a new and effective treatment for severe alcohol addiction, and potentially other types of addiction.

Still, "we want to be really careful in overstating or generalizing the other addictions," she noted. "In particular, it would have to be carefully studied for any kind of stimulant addiction because that is so involved directly in the dopamine pathways. We think there might be generalization to some addictions, but there could be more adverse effects with other types of drugs that a person might be using chronically."

More information: Gene therapy for alcohol-use disorder, *Nature Medicine* (2023). DOI: 10.1038/s41591-023-02470-w