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Two-drug combination has potential to fight cocaine addiction: study

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A fine-tuned combination of two existing pharmaceutical drugs has shown promise as a potential new therapy for people addicted to cocaine—a therapy that would reduce their craving for the drug and blunt their symptoms of withdrawal.

In laboratory experiments at The Scripps Research Institute, the potential therapy, which combines low doses of the drug naltrexone with the drug buprenorphine, made laboratory rats less likely to take cocaine compulsively—a standard preclinical test that generally comes before human trials.

While the two-drug combination would have to prove safe and effective for people in clinical trials before approval by the U.S. Food and Drug Administration (FDA), the work represents a significant advance in the field because there are currently no FDA-approved medications for treating cocaine addiction.

Many individual drugs have been tried in clinical trials in the past as potential treatments, but they have all failed to show significant efficacy in treating people addicted to cocaine, said Scripps Research Professor George Koob, chair of the Scripps Research Committee on the Neurobiology of Addictive Disorders and team leader for the research, which appears this week in the journal *Science Translational Medicine*.

"Combining drugs with multiple actions may be a useful approach that has not been utilized extensively," Koob said.

"These findings potentially represent a huge bridge from basic research to the establishment of a new and effective medication for cocaine addiction," added Senior Research Associate Leandro F. Vendruscolo, a co-author on the study with Scripps Research colleagues Assistant Professor Sunmee Wee (first author), former Research Associate Kaushik Misra, and Research Associate Joel Schlosburg.

Cocaine and the Brain's Reward System

Cocaine abuse is a major problem in the United States, and an Office of National Drug Control Policy study that came out in the mid-1990s estimated that Americans spend more on cocaine than on all other illegal drugs combined. The National Institute on Drug Abuse estimated that in 2008 1.9 million Americans had used cocaine within the last month. About a quarter of all drug-related emergency room visits are linked to cocaine use—482,188 in 2008 alone.

How doctors think about treating people addicted to cocaine and other drugs has evolved in the last generation as they have come to better understand how these substances affect the brain's physiology. Where once treatment for addiction focused solely on therapy, counseling, and other forms of social support, treatment today for many types of addiction combines those traditional approaches with anti-stress medications and other pharmaceuticals that directly address the long-term physiological effects of a drug on the body.

Koob and his colleagues have been at the forefront of this revolution in our understanding of the prolonged effect of drug abuse on the brain.

When cocaine, a chemical salt extracted from the leaf of the coca plant, is snorted, injected, or smoked, the chemical enters the bloodstream and readily crosses the blood–brain barrier, accumulating rapidly in areas linked to the so-called motivational/pleasure circuits of the brain.

There, the cocaine molecules interfere with the normal regulation of dopamine by binding to dopamine transporters and blocking them from recycling the neurotransmitter. This leads to the build-up of dopamine in the brain's motivational systems, which produces a euphoric feeling in the user—a quick rush that hits seconds after the user takes the drug and lasts several minutes. This physiological action triggers opposing actions in the brain, one of which is increases in a neuropeptide dynorphin that produces stress/aversive like effects (effectively an opponent process).

What Koob and his colleagues have demonstrated over the last several years is that excessive and prolonged cocaine use changes the point at which this euphoria is achieved, at least in part by activating these stress/aversive systems in the brain. Over time, it takes more of the drug to achieve the same effect, and after cocaine use is stopped, stress and aversion remains elevated.

In a paper in Psychopharmacology in 2009, the team showed two different systems (kappa opioid system and mu receptor) had different effects on the cocaine intake of rats with short versus extended access to the drug. "This finding gave us a firm idea that, during extended access to cocaine, the positive brain reward function becomes attenuated while the negative brain stress/aversive systems get involved," said Wee.

Consequences of this resetting include the withdrawal and cravings people addicted to cocaine feel when they stop the drug. These negative emotional/aversive effects drive relapse—an unfortunate reality for many addicts who try to quit—because drug use can temporarily alleviate their negative symptoms.

A Combination Approach

The idea behind treating drug addiction with pharmaceuticals is to restore the brain's reward and stress/aversive systems to normal, and the

new study explored how combining two existing pharmaceuticals might achieve that purpose: one that doesn't work on its own and one that works but is not prescribed because it is itself addictive.

Naltrexone is already approved by the FDA for treating alcohol and tobacco addiction.

Buprenorphine is an opiate—a painkiller similar to morphine or heroin—and it is known to be effective at helping people who are addicted to both heroin and cocaine kick their combined drug habits because it has mu opioid partial agonist effects (moderately produces the pleasurable effects of opioids) and kappa opioid antagonist effects (reverses the stress/aversive-like effects of opioid withdrawal by blocking the actions of dynorphin).

However, buprenorphine itself produces dependence and it is generally not prescribed unless someone is already addicted to a similar opiate, like heroin. The danger is that treating cocaine addiction with buprenorphine would merely substitute one dependence for another, causing people to suffer from buprenorphine withdrawal instead of cocaine withdrawal.

The Scripps Research team found a way around this problem by combining buprenorphine with a low dose of naltrexone, showing that giving rats this combination effectively blocked compulsive cocaine self-administration without causing the physical opioid withdrawal syndrome seen in rats treated with buprenorphine alone.

More information: "A Combination of Buprenorphine and Naltrexone Blocks Compulsive Cocaine Intake in Rodents Without Producing Dependence," *Science Translational Medicine*, 2012.

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