

Blocking glutamate release reduces oxycodone intake and seeking behavior

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Over the last decade, opioid abuse and overdoses have reached epidemic proportions in the United States. Now, Scripps Research scientists show that a drug that activates metabotropic glutamate 2 receptors in the brain can reduce oxycodone intake and drug-seeking behavior in an animal model of opioid use disorder (OUD).

Importantly, the drug was able to reduce [oxycodone](#) intake and relapse without disrupting other reward responses in the brain, which could result in [negative side effects](#). The team published their findings on July 20, 2023, in the journal *Neuropharmacology*.

[OUD is estimated](#) to impact more than two million people in the U.S. alone, and more than 70,000 people die of [opioid overdoses](#) each year. Semi-synthetic opioids, such as oxycodone, are responsible for almost 20 percent of these deaths. Current OUD treatments, such as methadone, buprenorphine and naltrexone are effective in the short-term, but many patients relapse, and better treatment options are urgently needed.

"Our research demonstrates that targeting the glutamate system with novel pharmacotherapies can stop oxycodone self-administration and seeking in preclinical models, which supports this approach as a future potential treatment for prescription opioid use disorder," says study senior author Rémi Martin-Fardon, Ph.D., associate professor in the Department of Molecular Medicine at Scripps Research.

The therapeutic tested, ADX106772, is produced by Addex Therapeutics and works by activating the mGlu2 receptor. These receptors inhibit the release of glutamate and are expressed in brain regions associated with addiction.

"Drugs of abuse all illicit glutamate release in the brain," says Jessica Illenberger, Ph.D., first author of the study and a postdoctoral research associate in the Martin-Fardon lab. "By reducing the release of glutamate, our study was designed to thereby reduce the effects of the drug and withdrawal on the brain."

Other drugs that work via similar mechanisms have been shown to effectively decrease the intake of other addictive substances—including cocaine, alcohol and nicotine—but this study is the first demonstration

that this class of pharmaceuticals might also be effective in combatting opioid use.

To test whether ADX106772 could reduce opioid intake, the researchers first trained [rats](#) to self-administer oxycodone by pressing a lever. The rats were also conditioned to associate an auditory and [visual cue](#) with oxycodone availability: When oxycodone was delivered, a light above the lever lit up while white noise played in the background. Exposure to drug-associated stimuli is known to set off circuits in the brain that cause craving, so training the rats to associate these cues with oxycodone—analogue to drug paraphernalia—allowed the researchers to model how drug-seeking behavior and relapse are prompted by drug-associated cues.

Once the rats were dependent on oxycodone, the researchers tested whether administering ADX106772 reduced their oxycodone intake. They found that ADX106772 significantly reduced self-administration of oxycodone for upwards of 12 hours. Higher doses of ADX106772 were associated with a faster onset of action.

The researchers also tested whether ADX106772 could help prevent relapse. To do this, they first induced abstinence by stopping access to oxycodone so when the rats pressed the lever, no oxycodone was administered and the light no longer lit up.

"When we take away both the oxycodone and the cue associated with it, the rat essentially learns there's no reason to push the lever anymore," says Illenberger. "Just reintroducing the cue that was previously associated with the drug of abuse is powerful enough to get them to seek the drug and press the lever, even if there's still no drug being delivered."

However, when the rats received ADX106772, they were much less likely to display this drug-seeking behavior when reintroduced to the

drug-associated cues, indicating that the therapeutic might be useful for both reducing oxycodone intake and preventing relapse.

To ensure that ADX106772's effect was selective in reducing oxycodone intake, the researchers also tested whether it impacted the rats' intake of a non-drug reward—sweetened condensed milk. They found that ADX106772 did not affect the rats' intake or seeking of sweetened condensed milk, indicating that its effects do not impact other natural reward systems.

"Whenever we're looking at therapeutics for drug abuse, we want to make sure that the therapeutic is only reducing drug-seeking and not reducing the seeking of other things that the individual finds rewarding, like food or sex. This could cause other problems, such as depression," says Illenberger.

Because opioid use disorder is characterized by drug craving that persists for a long time after abstinence, repeated or chronic treatment with ADX106772 may be necessary to prevent relapse in the long-term. Though short-term treatment with ADX106772 did not impact food-seeking behavior, future studies are needed to test the potential effects of chronic treatment on off-target behaviors.

"Knowing that modulating the glutamergic system has been shown to successfully block nicotine, cocaine, and alcohol-motivated behaviors, our study strongly suggests that targeting mGlu2 receptors to decrease glutamate release could be an umbrella treatment for excessive [drug](#) use and relapse," says Martin-Fardon.

In addition to Illenberger and Martin-Fardon, authors of the study "ADX106772, an mGlu 2 receptor positive allosteric modulator, selectively attenuates oxycodone taking and seeking," include Francisco J. Flores-Ramirez, and Alessandra Matzeu of Scripps Research; and

Robert Lütjens of Addex Pharmaceuticals.

More information: Jessica M. Illenberger et al, ADX106772, an mGlu2 receptor positive allosteric modulator, selectively attenuates oxycodone taking and seeking, *Neuropharmacology* (2023). [DOI: 10.1016/j.neuropharm.2023.109666](https://doi.org/10.1016/j.neuropharm.2023.109666)

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