

# Fast-fail trial shows new approach to identifying brain targets for clinical treatments

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A first-of-its-kind trial has demonstrated that a receptor involved in the brain's reward system may be a viable target for treating anhedonia (or lack of pleasure), a key symptom of several mood and anxiety disorders.

This innovative fast-fail trial was funded by the National Institute of Mental Health (NIMH), part of the National Institutes of Health, and the results of the trial are published in *Nature Medicine*.

Mood and anxiety disorders are some of the most commonly diagnosed mental disorders, affecting millions of people each year. Despite this, available medications are not always effective in treating these disorders. The need for new treatments is clear, but developing psychiatric medications is often a resource-intensive process with a low success rate. To address this, NIMH established the Fast-Fail Trials program with the goal of enhancing the early phases of drug development.

"The fast-fail approach aims to help researchers determine—quickly and efficiently—whether targeting a specific neurobiological mechanism has the hypothesized effect and is a potential candidate for further clinical [trials](#)," explained Joshua A. Gordon, M.D., Ph.D., director of NIMH. "Positive results suggest that targeting a neurobiological mechanism affects brain function as expected, while negative results allow researchers to eliminate that target from further consideration. We hope this approach will pave the way towards the development of new and better treatments for individuals with mental illnesses."

In this study, researcher Andrew D. Krystal, M.D.—who began the research while at the Duke University School of Medicine, Durham, North Carolina, and is now at the University of California, San Francisco—and colleagues report the first comprehensive application of this fast-fail approach. The researchers examined the kappa opioid receptor (KOR) as a possible neurobiological target for the treatment of anhedonia. Previous findings suggest that drugs that block the KOR, known as KOR antagonists, can affect reward-related brain circuits in ways that could improve reward processing and reverse anhedonia and associated symptoms.

The researchers conducted an eight-week double-blind, randomized placebo-controlled trial with 86 participants across six clinical sites in the United States. Participants were eligible if they were 21 to 65 years old, met the criteria for clinically significant anhedonia and the diagnostic criteria for a mood or anxiety disorder, and did not have other medical or psychiatric conditions. Participants were randomly assigned to receive either a 10 mg dose of the KOR antagonist JNJ-67953964 (previously CERC-501 and LY2456302) or an identical-looking placebo tablet. They received one dose daily over the eight-week trial.

To measure the effects of the KOR antagonist, the researchers examined the activation of the ventral striatum, a structure located in the middle of the brain that is involved in decision making, motivation, reinforcement, and reward. Participants completed a reward anticipation task while their brain activity was measured in a functional MRI scanner. During the task, participants saw a cue that signaled whether the upcoming trial might lead to [monetary gain](#), monetary loss, or neither. In some trials, participants had an incentive to press a specific button, as they could gain money or avoid losing money by doing so. They completed the task once at the beginning and again at the end of the trial.

Relative to those who received the placebo, participants who received the KOR antagonist showed increased activation in the ventral striatum when anticipating monetary gain (versus no-incentive trials). Additional analyses indicated that participants who received the KOR antagonist also showed greater activation of the ventral striatum during anticipation of loss.

Exploratory analyses indicated that lower ventral striatum activation in anticipation of monetary gain at baseline was associated with greater change in activation over the course of the trial, and this correlation was strongest for those who received the KOR antagonist. According to the researchers, this finding suggests that baseline ventral striatal activation

may have promise as a neurobiological marker that identifies participants who are most likely to respond to the KOR antagonist. Further analyses suggest that the KOR antagonist also had observable effects on secondary behavioral and self-report measures, including decreased anhedonia scores.

"Together, these findings demonstrate that the KOR antagonist had the hypothesized effect on brain circuits involved in reward and pleasure, establishing proof of mechanism," explained Dr. Krystal. "The results provide support for the usefulness and feasibility of fast-fail trials and—more specifically—for KOR antagonism as a potential target for drug development."

Further testing in larger trials will allow researchers to examine whether using KOR antagonism to engage the [ventral striatum](#) yields observable therapeutic effects on anhedonia and related clinical outcomes.

"This study was the first successful implementation of the fast-fail approach and it serves as a proof of principle of the viability of this methodology," says Mi Hillefors, M.D., Ph.D., acting deputy director of NIMH's Division of Translational Research. "We hope that the knowledge gained from the study will lead to more informative treatment trials in the future, contribute to the field of psychopharmacology, and reduce the risks typically associated with developing new psychiatric medications."

**More information:** A randomized proof-of-mechanism trial applying the 'fast-fail' approach to evaluating  $\kappa$ -opioid antagonism as a treatment for anhedonia, *Nature Medicine* (2020). [DOI: 10.1038/s41591-020-0806-7](#) , [nature.com/articles/s41591-020-0806-7](https://www.nature.com/articles/s41591-020-0806-7)

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