

Does Paxlovid Reduce Long COVID Symptoms? Yale-Led Trial Finds Out

Paxlovid may not reduce the symptoms of Long COVID, but a new trial format eased participant burden.

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Antiviral medications nirmatrelvir/ritonavir (Paxlovid) were not effective in relieving Long COVID symptoms, according to a new study published in [The Lancet Infectious Diseases](#) on April 3.

The findings came from the [Yale Paxlovid for Long COVID \(PAX LC\) Trial](#), led by principal investigator [Harlan Krumholz, MD](#), Harold H. Hines, Jr. Professor of Medicine (Cardiology), and [Akiko Iwasaki, PhD](#), Sterling Professor of Immunobiology.

The phase 2 investigational new drug clinical trial tested whether a 15-day course of Paxlovid, an FDA-approved antiviral for acute COVID-19, could also help Long COVID patients. The PAX LC team pioneered [a novel, decentralized design](#) that brought the trial into 100 participants' homes around the nation. It's the first fully decentralized phase 2 trial of its scale, the researchers say.

"This is the first time that we've been able to execute on a study that enrolled people throughout the entire contiguous United States in a manner that was convenient and easy for them," says Krumholz. "We got an answer that, though disappointing, at least provides more information for us to continue the effort to try to help relieve suffering among these individuals."

The trial was based on one of experts' [four hypotheses](#) on what causes Long COVID. In a subset of individuals, they speculate, persistent SARS-CoV-2 virus may continue to replicate in the body even after the initial COVID-19 infection. Although there have been case reports that some patients taking longer-term Paxlovid (beyond the standard five-day course for acute infections) experienced symptom relief, at the time of starting the PAX LC Trial, there had been no other clinical trials testing the antiviral's efficacy in treating the post-acute infection syndrome.

Bringing PAX LC into participants' homes

Participation in the PAX LC Trial was open to anyone nationwide who experienced any Long COVID symptoms—such as fatigue, weakness, and brain fog—within four weeks of having a positive COVID-19 test. All participants shared their medical records through Hugo Health, a platform co-founded by Krumholz that allowed the researchers to access the medical files electronically within

a matter of minutes and ensure the individual's eligibility while protecting their privacy. In total, 100 people joined the study.

Once cleared and enrolled, the participants received by mail their 15-day course of either Paxlovid or a placebo. Each day, they described their symptoms in electronic diaries from their phones or computers to be transmitted to a trial database to be reviewed by the research team. Medical professionals collected blood and saliva samples either at the participants' homes or at a local laboratory. After 28 days, they reassessed Long COVID symptoms.

Krumholz is especially excited about the PAX LC Trial's novel format, which eased the burden of participating in a clinical trial. "For people who were highly disabled by Long COVID we made it so they didn't have to find transportation or make repetitive site visits," he says. "We designed the trial with them in mind and with their input, and we made a strong commitment to ensure that we were attentive to their needs throughout every phase of the trial."

After publishing the study, the investigators also held a virtual town hall available to all participants. "We wanted them to be among the very first to hear the results and have the opportunity to ask the investigators questions," he says.

Paxlovid fails to improve long COVID symptoms

The study found that Paxlovid did not cause any significant changes in symptoms across the cohort. Other clinical trials have reported similar results, including the STOP-PASC Trial at [Stanford Medicine](#).

But while the antiviral did not benefit the group as a whole, Long COVID is likely caused by several different mechanisms. One [recent case study published in Nature](#) involved 13 patients who took an extended course of Paxlovid ranging from 7.5 to 30 days, and showed variable results—five reported lasting improvement [reduction of symptoms lasting months after treatment], four temporary improvement [returned to baseline weeks/months after treatment], and four no improvement.

While there were no significant differences in the symptoms reported by the Paxlovid vs. placebo arms, individual participants experienced varying outcomes. In future research, Iwasaki hopes to better understand this variation. Her lab team is continuing to conduct detailed analyses of participants' immune systems based on the collected blood samples and plans to publish the results later in the year. "Even if there are only one or two people who truly experienced benefit, we want to understand what the biological mechanisms might be by looking at the immune signatures," she says.

Furthermore, there might be ways to tweak the PAX LC Trial protocol so that more people may benefit. "The case study goes on to show that maybe the duration of the drug wasn't long enough, or maybe our selection criteria should be different," she says. "There are lots of reasons why a clinical trial fails, but it's still important for us to be able to say that this particular regimen wasn't

effective when compared to a placebo.”

To evaluate the impact of the decentralized trial design, the researchers also asked participants to rate their experiences on a scale of one to 10. The average overall satisfaction rating was 7.9, the study’s team friendliness was rated at 8.1, and the likelihood of referring others to PAX LC or a similar study was 8.3.

Benefits of decentralized clinical trials

The researchers are disappointed that Paxlovid did not provide relief to the participants. However, they are optimistic that the PAX LC Trial is proof that decentralized trials are not only immensely beneficial to the participants but can also be conducted in an efficient and cost-effective way. “We hope to use this platform for any future studies that don’t require a doctor’s visit for drug treatment,” Iwasaki says.

The participant satisfaction also emphasizes the importance of making clinical trials accessible, Krumholz adds. Noting that it is unusual to report on the experiences of people within a clinical trial, he explains, “I insisted with the journal we published in that we include a metric that showed how satisfied people were with the trial.

“This is a group that’s frustrated because they’re very sick,” says Krumholz. “Many of them have been dismissed by the medical care system—so it’s understandable that they’re not optimistic. But their ratings of their experience in this trial were exceptionally high.”

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