Trial shows a faster approach for starting extended-release naltrexone to treat opioid use disorder is effective

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Starting people with opioid use disorder on extended-release, injectable naltrexone (XR-naltrexone) within five to seven days of seeking treatment is more effective than the standard treatment method of

starting within 10–15 days, but requires closer medical supervision, according to results from a clinical trial published in *JAMA Network Open*.

The findings suggest that this rapid treatment protocol could make XR-naltrexone more viable as a treatment option for opioid use disorder, which continues to take lives at an alarming rate.

"When someone is ready to seek treatment for opioid use disorder, it is crucial that they receive it as quickly as possible," said Nora Volkow, M.D., National Institute on Drug Abuse director. "This study paves the way for more timely care with one of the three medications for opioid use disorder we have available, better supporting people in their ability to choose the treatment option that will work best for them."

XR-naltrexone is one of three Food and Drug Administration-approved medications for the treatment of opioid use disorder. It works by binding to and blocking opioid receptors in the brain, which reduces opioid cravings and prevents the euphoric and sedative effects of opioids.

However, starting treatment with XR-naltrexone has traditionally required patients to go through a seven to 10-day opioid-free period, to avoid experiencing painful withdrawal symptoms caused when naltrexone abruptly stops the effects of opioids in the brain. During this waiting period, patients are at high risk of returning to opioid use or discontinuing treatment. This has been a significant barrier to implementation of XR-naltrexone.

To address this challenge, researchers tested the effectiveness of a more rapid procedure to start people with opioid use disorder on XR-naltrexone. Between March 2021 and September 2022, the study enrolled and followed 415 patients with opioid use disorder who were admitted at six community-based inpatient addiction facilities across the

U.S. and who chose treatment with XR-naltrexone. Every 14 weeks, the sites were randomized to either provide the standard XR-naltrexone procedure, or the more rapid procedure.

In the study, standard XR-naltrexone prescribing included a three- to five-day treatment period with buprenorphine to ease withdrawal symptoms, followed by a seven- to 10-day opioid-free period. The rapid procedure consisted of one day of buprenorphine (up to 10 mg), a 24-hour opioid-free period, and a gradual increase in low-dose oral naltrexone for three to four days prior to getting an injection of XR-naltrexone. Doctors also used medications such as clonidine and clonazepam throughout the process to manage withdrawal symptoms.

The study found that patients on the rapid five to seven-day treatment procedure were significantly more likely to receive a first injection of XR-naltrexone compared to those on the standard seven to 15-day treatment procedure (62.7% vs. 35.8%). Withdrawal severity was generally low and comparable across the two groups. Targeted safety events and serious adverse events (such as a fall or overdose) were infrequent overall but occurred more on rapid procedure (5.3% and 6.7%) than on standard procedure (2.1% and 1.6%), and the rapid procedure required more staff attention. This indicates that closer monitoring and greater clinical expertise may be needed if patients start treatment with the rapid procedure.

Though the shorter wait-time improved the proportion of people who started on XR-naltrexone overall, these findings underscore that challenges remain in starting patients on XR-naltrexone and also keeping them in treatment long term. Across both the standard and rapid procedures, the most commonly reported reason that participants did not receive a first dose of XR-naltrexone was that they chose to leave the treatment unit early.

The authors also note that only about 10% of all patients entering treatment chose XR-naltrexone. These findings reaffirm that a small but sizable proportion of people with opioid use disorder do opt for treatment with XR-naltrexone when presented with all three medication choices, and that it is important to support research into making this evidence-based treatment option more viable for those who choose it.

"Time has been an important barrier that we've seen hinder the use of extended-release naltrexone for opioid use disorder in the past, both among individuals and treatment providers," said Matisyahu Shulman, M.D., a clinician researcher at New York State Psychiatric Institute and Columbia University Irving Medical Center, New York City, and lead author on the study. "We hope that these findings can help encourage more treatment settings to offer extended-release naltrexone as a safe and effective option for patients, to help prevent overdose and support recovery."

The authors note that future studies should explore sustainability, feasibility, and health economic aspects of this more rapid treatment protocol for XR-naltrexone. Despite cost savings from fewer days on the rapid procedure, the resources needed for intensive monitoring should also be considered.

In 2022, over 107,000 people died of a drug overdose, with 75% of those deaths involving an opioid. The overall rise in overdose deaths is largely attributable to the proliferation in the drug supply of illicit fentanyl, a highly potent synthetic opioid. Decades of research have shown the overwhelming benefit of three existing medications for opioid use disorder: methadone, buprenorphine, and XR-naltrexone.

The study, known as the Surmounting Withdrawal to Initiate Fast Treatment with Naltrexone (SWIFT) study, was conducted at six sites within the NIDA Clinical Trials Network. The work was led by

researchers at New York State Psychiatric Institute and Columbia University Irving Medical Center.

More information: Rapid Initiation of Injection Naltrexone for Opioid Use Disorder: A Stepped-wedge, 8 Cluster-Randomized Clinical Trial, *JAMA Network Open* (2024). jamanetwork.com/journals/jaman … tworkopen.2024.9744?

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