National Institute on Drug Abuse

FOR IMMEDIATE RELEASE
January 13, 2020
5:00 p.m. Eastern

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Combination treatment for methamphetamine use disorder shows promise in NIH study

A combination of two medications, injectable naltrexone and oral bupropion, was safe and effective in treating adults with moderate or severe methamphetamine use disorder in a double-blind, placebo-controlled Phase III clinical trial. The findings suggest this combination therapy may be a promising addition to current approaches to treatment, such as cognitive behavioral therapy and contingency management interventions, for a very serious condition that remains difficult to treat and overcome. The research, published today in *The New England Journal of Medicine*, was conducted at multiple sites within the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN). NIDA is part of the National Institutes of Health.

"The opioid crisis and resulting overdose deaths in the United States are now well known, but what is less recognized is that there is a growing crisis of overdose deaths involving methamphetamine and other stimulants. However, unlike for opioids, there are currently no approved medications for treating methamphetamine use disorder," said NIDA Director Nora D. Volkow, M.D. "This advance demonstrates that medical treatment for methamphetamine use disorder can help improve patient outcomes."

The study known as the Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder study, or ADAPT-2, was conducted from 2017 to 2019 at clinics in multiple community treatment programs nationwide and enrolled 403 adult volunteers ages 18 to 65 years with moderate to severe methamphetamine use disorder. All participants wished to reduce or cease use of the drug and were randomly assigned to the treatment or control group.

In each of two six-week stages, volunteers in the treatment group were given an injection of extended-release naltrexone, a drug used to treat opioid and alcohol use disorders, every three weeks and took daily extended-release tablets of bupropion, an antidepressant also used as a treatment to aid nicotine cessation. Those in the control group were given matched injectable and oral placebos over the same time periods. Investigators performed four urine drug screens at the end of each stage of the trial. Participants were considered to have responded to treatment if at least three of four urine screens were negative.

Overall, participants responded at a significantly higher rate in the treatment group. When screened during weeks five and six, 16.5% of those given the naltrexone/bupropion combination responded, compared to only 3.4% of those in the control group. Similarly, when screened in weeks 11 and 12, 11.4% of the treatment group responded, compared to 1.8% of the control group. Researchers calculated that the number needed to treat (NNT) was 9. NNT is a way to describe the utility of a medical intervention that indicates the number of people who would need to receive a treatment for it to benefit one person. The investigators reported that, with an NNT of 9, naltrexone/bupropion's benefit as a treatment for methamphetamine use disorder is similar

to most medical treatments for mental health disorders, including antidepressants prescribed for depression or naltrexone prescribed for alcohol use disorder.

Participants in the treatment group were assessed to have fewer cravings than those in the placebo group and reported greater improvements in their lives as measured by a questionnaire called the Treatment Effectiveness Assessment. Importantly, there were no significant adverse effects associated with the dual medication treatment. Adherence to treatment was encouraged by adherence counseling and mobile app reminders and remained high at 77.4% and 82.0% in the treatment and placebo groups, respectively, in the final six weeks of the study.

“Long-term methamphetamine misuse has been shown to cause diffuse changes to the brain, which can contribute to severe health consequences beyond addiction itself,” said Madhukar H. Trivedi, M.D., of the University of Texas Southwestern Medical Center, Dallas, who led the trial. “The good news is that some of the structural and neurochemical brain changes are reversed in people who recover, underscoring the importance of identifying new and more effective treatment strategies.”

Methamphetamine use disorder is a serious illness often associated with severe medical and mental health complications and a risk of fatal overdose. Methamphetamine is a potent stimulant, and, like other addictive drugs, it hijacks the reward pathways in the brain by raising levels of dopamine, a brain chemical associated with repeating actions that cause pleasurable feelings.

Finding treatments that disrupt these processes has been challenging for scientists. Research suggests bupropion may alleviate dysphoria associated with methamphetamine withdrawal by acting on the dopamine and norepinephrine systems. Alleviating dysphoria may in turn reduce cravings and help prevent return to methamphetamine use. Naltrexone may reduce the euphoric effects and cravings associated with taking methamphetamine. In previous clinical studies, however, both bupropion and naltrexone administered alone showed limited, inconsistent efficacy in treating methamphetamine use disorder. Now, in combination, these compounds seem to have an additive or synergistic effect.

While there are U.S. Food and Drug Administration-approved medications for other substance use disorders, no medications have yet received FDA approval for methamphetamine use disorder. The effectiveness of this medication combination is progress toward improving treatment of this addiction.

The investigators recommend that future research build on this work by testing if longer naltrexone/bupropion treatment or concurrent behavioral therapy, such as contingency management, brings still better responses. Contingency management, which uses motivational incentives and tangible rewards to help a person attain their treatment goals, has demonstrated to be the most effective therapy for stimulant use disorders but is not widely used, stemming in part from a policy limiting the monetary value of incentives allowable as part of treatment.

Trivedi MH, *et al*. **Trial of Bupropion and Naltrexone in Methamphetamine Use Disorder.** *New England Journal of Medicine*. January 14, 2020.

This work was funded by NIDA, as well as contracts supported by the U.S. Department of Health and Human Services.

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