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Combination drug targeting opioid system may help relieve treatment-resistant depression

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A clinical trial of an experimental drug for treatment-resistant major depression finds that modulation of the endogenous opioid system may improve the effectiveness of drugs that target the action of serotonin and related monoamine neurotransmitters. In their paper published online in the *American Journal of Psychiatry*, a multi-institutional research team reports that adding treatment with ALKS-5461, a medication that combines two drugs with complementary effects on different opioid receptors, to serotonin-targeting antidepressant therapy produced significant symptom improvement in patients with persistent depression. ALKS-5461 is being developed by Alkermes, Inc., which sponsored the trial.

"We know that more than half of patients with major depression won't respond to the first antidepressant they try, and almost 40 percent will continue to have symptoms even after switching to or adding different drugs," says Maurizio Fava, MD, executive director of the Clinical Trials Network & Institute in the MGH Department of Psychiatry and lead author of the study. "Opioids have actually been used for centuries to treat mood disorders, and while opioid drugs must be used cautiously because of their potential for abuse, studies have shown that levels of the endogenous opioids released by the central nervous system may be reduced in important brain areas of patients with major depression."

Opioid drugs produce their effects by binding to receptors in the

endogenous opioid system, which the body uses to suppress pain and to reward biologically beneficial activities. Two prominent opioid receptors are the mu and kappa receptors, which have overlapping but somewhat different effects. ALKS-5461 is a combination of buprenorphine, which suppresses kappa receptor activity and weakly activates mu receptors, and samidorphan, which blocks mu receptor activity. While buprenorphine is FDA-approved to help treat opioid addiction by easing withdrawal symptoms, samidorphan is an experimental drug being developed by Alkermes for several potential uses. The combination of the two drugs is an effort to balance the opioid system activity while avoiding adverse effects, including the potential for abuse.

The current study, a phase 2 clinical trial, enrolled 142 patients with treatment-resistant depression at 31 sites in the U.S. Since depression treatment trials are likely to have a large placebo response, this study used a design developed in 2003 by Fava and David Schoenfeld, PhD, an MGH biostatician, to reduce the impact of the placebo effect. Using this sequential parallel comparison design (SPCD), the trial was conducted in two stages. In stage 1, 98 participants were randomized to receive placebo doses while 43 participants received ALKS-5461 in daily dosages containing either 2 mg or 8 mg of each of the two drugs.

After the first four-week treatment period, placebo group members who did not show a response to treatment were re-randomized either to receive one of the two dosages of the active drug or to continue receiving a placebo for stage 2. Fava explains that, by manipulating the expectations of both participants and investigators—neither of which knew whether and when an individual was receiving the active drug—SPCD minimizes the likelihood of a placebo response, while reducing the need for a much large group of participants.

While both dosage levels of ALKS-5461 produced a greater reduction in depression symptoms than did the placebo, as measured by several

standard scales, the lower dosage of 2 mg of each drug had effects that were stronger and met statistical significance. Fava notes that it is not unusual for lower doses of psychotropic drugs to be more effective, since higher doses may have more side effects. The most common reported adverse events were nausea, vomiting and dizziness, most of which occurred during the first few days of treatment; and there was no evidence of withdrawal after the treatment period ended or of the likelihood of abuse of ALKS-5461.

"The robust treatment effect seen in this clinical study suggests that many patients with depression may have a dysregulation of the endogenous opioid system, which may be why they do not respond to monoamine-based antidepressants that target the serotonin system," says Fava, who is director of the Division of Clinical Research of the MGH Research Institute and the Slater Family Professor of Psychiatry at Harvard Medical School. "For the substantial percentage of patients who do not respond to monoamine based medications, this combination may represent an important new approach to the treatment of depression." Alkermes has been conducting three phase 3 studies of ALKS-5461, two of which have been completed but their results not yet reported in scientific journals.

More information: *American Journal of Psychiatry*, dx.doi.org/10.1176/appi.ajp.2015.15070921

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