Combination drug targeting opioid system may help relieve symptoms of major depression

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Two clinical trials of an investigational drug that targets the opioid system support its safety and effectiveness in reducing symptoms of

major depression, when added to standard antidepressant treatment. The results of these Phase 3 trials of a drug combining buprenorphine with samidorphan are reported today in *Molecular Psychiatry* by a research team led by a Massachusetts General Hospital physician.

"Less than 40 percent of patients with major depression achieve symptom remission from first-line treatment with today's antidepressant drugs, which target monoamine-based neural signaling," explains Maurizio Fava, MD executive director of the Clinical Trials Network & Institute in the MGH Department of Psychiatry and senior author of the *Molecular Psychiatry* report. "Having a new class of antidepressants with a novel mechanism of action could have significant impact for patients with persistent symptoms." Fava also led the Phase 2 trial of this drug combination, which was published in 2016 and identified the effectiveness of the highest dosage level tested in the current trials.

The endogenous opioid system—the neurological pathways that interact with opioid drugs—is believed to have a role in several factors that can be affected in clinical depression—including mood, motivation and social functions. PET imaging studies have suggested that opioid system circuits may be dysregulated in patients with major depression. While low doses of buprenorphine—an opioid used for both pain relief and in medication-assisted treatment for opioid addiction—had beneficial effects in a multicenter trial in patients with major depression, a major challenge to its use for depression treatment is the risk of abuse and dependence.

The combination of buprenorphine with samidorphan, which blocks one of the opioid receptors activated by buprenorphine, was designed to reduce the abuse and dependence potential of buprenorphine alone. The drug—also called ALKS 5461—is being developed by Alkermes, Inc., which sponsored the two trials, called FORWARD-4 and FORWARD-5, conducted at a total of 111 sites in several countries. FORWARD-4

compared two dosage levels—either 0.5 mg of each drug or 2.0 mg of each—with a placebo; and FORWARD-5 compared 1.0 mg and 2.0 mg doses with a placebo. A total of almost 800 adult patients who had not responded adequately to at least 8 weeks of antidepressant treatment enrolled and continued taking their standard antidepressant throughout the trial period.

Since trials of depression drugs often elicit a significant placebo effect, both trials were designed in a way to reduce that risk. During the first stage of both randomized trials, participants received their assigned doses of either the active drug or a placebo for 5 weeks, at the end of which they completed a standard depression symptom assessment. Although neither participants nor the research team members with whom they directly interacted knew individual patients' group assignments, other team members examined assessments from those receiving a placebo, identifying those in whom symptom reduction indicated a placebo effect.

Placebo group members who did not show symptom improvement were re-randomized either to continue receiving the placebo or to receive one of the tested doses of the active drug for the remaining 6 weeks of the trial. Again, they were not aware that their study medication had been changed. Other participants—both those receiving an active drug and those who were responding to the placebo—continued with the same medication during the second phase.

At the end of both trials, participants receiving the 2.0 mg doses of both active drugs had a greater reduction in depression symptoms than did those receiving a placebo. Those receiving 1.0 mg doses showed symptom reduction greater than the placebo group but less than the 2.0 mg doses, and the 0.5 mg-dose recipients had results no better than those of the placebo group. Although the differences between the 2.0 mg dosages and placebo in FORWARD-4 were not statistically significant,

combining the results from both trials produced a significant effect.

Reported adverse effects—such as nausea, sleepiness, dizziness and fatigue—were mild to moderate and usually disappeared within a few days. There were no reports of participants' taking excess doses, developing dependence or experiencing withdrawal symptoms. After their trial, participants were able to enroll in a long-term safety study of combined buprenorphine/samidorphan. Interim data from that study were presented at the American Psychiatric Association annual meeting in May 2018.

"Based on the safety profile observed with buprenorphine/samidorphan, we could have an important new pharmacological tool for patients with major depression who do not respond to standard therapies," says Fava, the Slater Family Professor of Psychiatry at Harvard Medical School.

More information: Maurizio Fava et al, Opioid system modulation with buprenorphine/samidorphan combination for major depressive disorder: two randomized controlled studies, *Molecular Psychiatry* (2018). DOI: 10.1038/s41380-018-0284-1

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