Brexpiprazole provides new second-line treatment options for patients with major depressive disorder

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Brexpiprazole, an antipsychotic drug approved this summer by the U.S. Food and Drug Administration, is an effective and well-tolerated addition to conventional first-line antidepressants for the treatment of major depressive disorder (MDD), according to research from psychiatrists in the Perelman School of Medicine at the University of

Pennsylvania. They detail their findings in two studies published this month in the *Journal of Clinical Psychiatry*.

"Although several other adjunctive therapies are FDA-approved for this indication, the side effects that come with these medications put them off-limits for many patients," said the study's lead author, Michael Thase, MD, a professor of Psychiatry and chief of the Mood and Anxiety Disorders section. "Since MDD is one of the world's great public health problems, it is gratifying to have new treatment options for patients who are not helped by current first- and second-line strategies."

A major depressive episode is defined by the National Institutes of Health (NIH) as a period of two weeks or longer during which patients experience a depressed mood or loss of interest or pleasure, and at least four other symptoms that reflect a change in functioning, such as problems with sleep, eating, energy, concentration, and self-image. Typically, symptoms caused by medical illness, bereavement, or substance abuse disorders are not considered MDD.

Both new studies, Phase 3 multicenter trials, enrolled patients who had a history of an inadequate response—defined by the authors as a less than 50 percent reduction in symptoms—to at least one and as many as three standard antidepressants.

The first study enrolled a total of 378 patients, all of whom who were all treated for eight weeks on a common antidepressant treatment. Patients with an inadequate response were then randomized to receive antidepressant therapy plus brexpiprazole (188), at a fixed dose of 2 mg/day, or antidepressant therapy plus placebo (191) for six weeks.

The researchers found that patients who received brexpiprazole showed a greater mean reduction in symptoms as measured by the Montgomery-Asberg Depression Rating Scale (MADRS), with the difference between

the groups apparent from the first day onward. Similar results were observed with regard to efficacy, with patients reporting improvements in work/school, social and family life.

The second study examined 677 patients randomized to brexpiprazole, at fixed doses of 3 mg/day (230) or 1mg/day (226), or placebo (221) for six weeks. Patients in the 3 mg group showed the most improvement based on MADRS scores versus placebo, whereas patients on brexpiprazole 1 mg did not. Patients who took Brexpiprazole at both the 1 mg and 3 mg doses showed greater improvement than those who took the placebo, however.

Importantly, researchers found the rate of one particular side effect, akathisia—agitation, distress, and restlessness—that can be a side-effect of some antipsychotic drugs, was low in both studies (about half the incidence observed in earlier studies of adjunctive therapy with aripiprazole, one of the most commonly used medications for adjunctive therapy in MDD). Rates of weight gain and drowsiness with brexpiprazole were similar to those observed in studies of aripiprazole, which suggests that the risk of akathisia was reduced without a compensatory increase in other side effects.

"Further studies will home in on the long-term tolerability of brexpiprazole so that we can further develop proper dosing guidelines," Thase said.

As a result of these studies, brexpiprazole was approved by the FDA on July 10, 2015 for the treatment of adults with schizophrenia and as an add-on treatment to an antidepressant medication to treat adults with major depressive disorder (MDD).

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