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Antipsychotic drug may be helpful treatment for anorexia nervosa

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Low doses of a commonly used atypical antipsychotic drug improved survival in a mouse model of anorexia nervosa, University of Chicago researchers report this month. The result offers promise for a common and occasionally fatal eating disorder that currently lacks approved drugs for treatment.

Mice treated with small doses of the drug olanzapine were more likely to maintain their weight when given an exercise wheel and restricted food access, conditions that produce activity-based anorexia (ABA) in animals. The antidepressant fluoxetine, commonly prescribed off-label for anorexic patients, did not improve survival in the experiment.

"We found over and over again that olanzapine was effective in harsher conditions, less harsh conditions, adolescents, adults — it consistently worked," said the paper's first author Stephanie Klenotich, graduate student in the Committee on Neurobiology at the University of Chicago Biological Sciences.

The study, published in Neuropsychopharmacology, was the product of a rare collaboration between laboratory scientists and clinicians seeking new treatment options for anorexia nervosa. As many as one percent of American women will suffer from anorexia nervosa during their lifetime, but only one-third of those people will receive treatment.

Patients with anorexia are often prescribed off-label use of drugs designed for other psychiatric conditions, but few studies have tested the

drugs' effectiveness in animal models.

"Anorexia nervosa is the most deadly psychiatric disorder, and yet no approved pharmacological treatments exist," said Stephanie Dulawa, PhD, assistant professor of Psychiatry & Behavioral Neuroscience at the University of Chicago Medicine and senior author of the study. "One wonders why there isn't more basic science work being done to better understand the mechanisms and to identify novel pharmacological treatments."

One challenge is finding a medication that patients with anorexia nervosa will agree to take regularly, said co-author Daniel Le Grange, PhD, professor of Psychiatry & Behavioral Neuroscience and director of the Eating Disorders Clinic at the University of Chicago Medicine. Drugs that directly cause weight gain or carry strong sedative side effects are often rejected by patients.

"Patients are almost uniformly very skeptical and very reluctant to take any medication that could lower their resolve to refrain from eating," Le Grange said. "There are long-standing resistances, and I think researchers and clinicians have been very reluctant to embark on that course, since it's just littered with obstacles."

Both fluoxetine and olanzapine have been tried clinically to supplement interventions such as family-based treatment and cognitive-behavioral therapy. But their direct effect on anorexia nervosa behavior — in humans or animals — is lacking in sufficient data.

To test the effectiveness of these drugs in laboratory mice, Klenotich adapted the ABA protocol from previously published rat studies: Mice given 24-hour access to a running wheel but only six hours a day of food access become hyperactive, eat less and rapidly lose weight, with a 25 percent reduction from baseline considered to be the "drop-out" survival

point.

In Klenotich's study, mice were pretreated with fluoxetine, olanzapine or saline before starting the ABA protocol, and treatment continued throughout the ABA period. Researchers then measured how many mice in each group reached the drop-out point for weight loss over 14 days of food restriction and exercise wheel access. Treatment with the antipsychotic olanzapine significantly increased survival over the control group, while fluoxetine treatment produced no significant effects on survival.

Importantly, a low dose of olanzapine did not decrease overall running activity in the mice, indicating that sedative effects of the drug were minimal. In future experiments, the researchers hope to use different drugs and genetic methods to determine exactly how olanzapine is effective against symptoms of anorexia nervosa, perhaps pointing toward a better drug without the negative image or side effects of an antipsychotic.

"We can dissect the effect of olanzapine and hopefully identify the mechanisms of action, and identify what receptor systems we want to target," Klenotich said. "Hopefully, we can develop a newer drug that we can aim towards the eating disorders clinic as an anorexic-specific drug that might be a little more acceptable to patients."

The study offers support for the clinical use of olanzapine, for which clinical trials are already under way to test in patients. Le Grange said the development of a pharmacological variant that more selectively treats anorexia nervosa could be a helpful way to avoid the "stigma" of taking an antipsychotic while giving clinicians an additional tool for helping patients.

"I think the clinical field is certainly very ready for something that is

going to make a difference," Le Grange said. "I'm not saying there's a 'magic pill' for anorexia nervosa, but we have been lacking any pharmacological agent that clearly contributes to the recovery of our patients. Many parents and many clinicians are looking for that, because it would make our job so much easier if there was something that could turn symptoms around and speed up recovery."

Additionally, the study demonstrated the innovative experimental design and translational results that can come from a collaboration of laboratory and clinical experts.

"We don't talk to one another often enough in basic science and clinical science," Le Grange said. "More of that would be helpful for clinicians to understand the neurobiology of this disease. I'm very excited about the way this project is going, and I think it's going to be clinically very informative."

More information: The paper, "Olanzapine, but not fluoxetine, treatment increases survival in activity-based anorexia in mice," was published online March 7 by *Neuropsychopharmacology* (doi: 10.1038/npp.2012.7).

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