

## Study makes progress toward shorter antidepressant reaction times

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Researchers at the University of Chicago and the University of Minho in Portugal say they have found a way to speed up the rate in which antidepressants take effect in mice to about five days. Antidepressant drugs for humans typically take two weeks or longer to become effective. (Lesley Magno, Getty Images / January 13, 2014)

**By Janice Neumann, Special to the Tribune**

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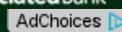
The typical antidepressant can take two weeks or more to work, putting some patients in the interim at risk of further psychological deterioration or even suicide, according to psychiatrists.

But researchers at the University of Chicago and University of Minho in Portugal said they have found a way to speed up the antidepressant process in mice with two compounds that block a cell receptor for serotonin, lifting depression in five days.

These compounds, called serotonin 2c receptor antagonists, function differently than standard antidepressants by increasing the firing rate of dopamine nerve cells. Other

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antidepressants tend to target serotonin nerve cells.

In addition to their antidepressant behavioral effects, these agents also created molecular and structural brain changes similar to those of other antidepressants.

Dopamine is a neurotransmitter that controls reward-motivated behavior and motor control, while serotonin is a neurotransmitter that regulates mood, memory and appetite.

"Essentially it likely changes functional connections in the brain in certain areas," said Stephanie Dulawa, senior author of the study and associate professor of psychiatry and behavioral neuroscience at the University of Chicago. "We looked specifically in areas called the medial prefrontal cortex, which is strongly implicated in depression in human studies, which makes it highly relevant."

The study examined the effects of the compounds in depressed mice. Researchers used a swimming test, in which the motivation to continue swimming was measured, and exposed them to mild stressors, such as putting them in a tilted cage while injecting them with a sucrose compound to see how much pleasure the mice derived from it while experiencing stress. They also removed the portion of the brain that affects a mouse's sense of smell, to mimic depression. In each case, depressive behavior decreased with administration of the compounds. Results were published Oct. 29 in the journal *Molecular Psychiatry*.

Dulawa said her work on identifying compounds acceptable for human use would likely take a few more years. The two serotonin 2c antagonists used in the study can be administered only to animals, she said. Two drugs that have antidepressant effects within hours to days are scopolamine and ketamine, but neither is approved for human use to treat depression because of side effects.

"It would be a huge breakthrough," said Dulawa. "A fast-acting antidepressant that would be safe would basically revolutionize the treatment of depression."

Dr. John Neumaier, professor of psychiatry and pharmacology at the University of Washington, said one strength of the study was its use of two compounds that targeted the production rate of different brain chemicals, which "increased the likelihood they are interpreting the data correctly." He also said the study was bolstered by using several different depression models with different outcomes.

"I think it's a very well-done study," said Neumaier. "It's very mechanistically driven, talking about not only shorter duration of action but different specific brain regions that might be involved, including dopamine and the prefrontal cortex, which is intriguing."

Neumaier also said the study might have important implications beyond shortening the onset of antidepressant effect.

"I think it's important we have drugs that have different mechanisms of action than the current ones. The antidepressants we have now don't always work," said Neumaier.

Dr. Carlos Zarate, who heads the Section on the Neurobiology and Treatment of Mood Disorders at the National Institute of Mental Health, said the research was an important contribution to the emerging field of fast-acting antidepressants, though he cautioned the results would need to be replicated in humans and that, ideally, new drugs would work in fewer than five days.

Zarate, who has done research on the antidepressant effects of ketamine and scopolamine, said finding fast-acting antidepressants is crucial because the disease can be so debilitating.

"I think other areas of medicine can rapidly control sugar, hypertension or even stroke very rapidly, but for people who are depressed ... antidepressants will take quite a bit of time to kick in there," said Zarate. "Imagine if you have something that works in a few hours or a few days, you can prevent all that sad stuff from happening."



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