

Antipsychotic drugs work differently than scientists believed

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Antipsychotic drugs—used to treat the millions of people in the U.S. with schizophrenia—have lots of unpleasant side effects. The drugs also aren't effective for many people. There is an urgent need to develop

better drugs.

A new finding from Northwestern Medicine scientists provides a new avenue to develop more effective drugs to treat the debilitating symptoms of [schizophrenia](#). Traditionally, researchers have screened antipsychotic [drug](#) candidates by evaluating their effects on mouse behavior, but the approach used by a Northwestern lab outperformed these traditional approaches in terms of predicting efficacy in patients.

The study discovered that antipsychotic drugs—which inhibit the overactive [dopamine](#) causing the symptoms of schizophrenia—interact with a completely different neuron than scientists originally believed.

"This is a landmark finding that completely revises our understanding of the neural basis for psychosis and charts a new path for developing new treatments for it," said lead investigator Jones Parker, assistant professor of neuroscience at Northwestern University Feinberg School of Medicine." It opens new options to develop drugs that have fewer adverse side effects than the current ones."

The study was recently published in *Nature Neuroscience*.

Individuals with schizophrenia have increased levels of dopamine in a region of the brain called the striatum. This region has two primary types of specialized brain cells called neurons: those that have D1 [dopamine receptors](#) and those that have D2 dopamine receptors.

Receptors on neurons are like locks waiting for the key that turns them on. Picture two populations of neurons, one that expresses locks called D1 receptors and the other called D2 receptors. Dopamine is a key for both receptors, but antipsychotics only block the D2 receptor locks. Therefore, experts have assumed these drugs preferentially act on neurons that express the D2 receptor locks. But, in fact, it was the other

[brain cells](#)—the neighboring ones in the striatum with D1 receptors—that responded to antipsychotic drugs in a manner that predicted clinical effect.

"The dogma has been that antipsychotic drugs preferentially affect striatal neurons that express D2 dopamine receptors," Parker said. "However, when our team tested this idea, we found that how a drug affects the activity of D2 receptor-expressing striatal neurons has little bearing on whether it is antipsychotic in humans. Instead, a drug's effect on the other striatal neuron type, the one that expresses D1 dopamine receptors, is more predictive of whether they actually work."

Schizophrenia is a debilitating brain disorder that affects approximately 1 in 100 people (more than 2.5 million people in the U.S.). While existing antipsychotics are effective for the hallmark symptoms of schizophrenia such as hallucinations and delusions, they are ineffective for the other symptoms of schizophrenia such as deficits in cognitive and social function.

Moreover, current antipsychotics are completely ineffective in more than 30% of patients with treatment-resistant schizophrenia (more than 750,000 people in the U.S.). The use of these drugs also is limited by their adverse effects, including tardive dyskinesia (uncontrollable body movements) and parkinsonism (rigidity, tremors and slowness of movement).

The new study for the first time determined how [antipsychotic drugs](#) modulate the region of the brain thought to cause psychosis in living animals.

"Our study exposed our lack of understanding for how these drugs work and uncovered new therapeutic strategies for developing more effective antipsychotics," Parker said.

Other Northwestern authors include first author Seongsik Yun, Ben Yang, Justin Anair, Madison Martin, Stefan Fleps, Arin Pamukcu, Nai-Hsing Yeh, Anis Contractor and Ann Kennedy.

The title of the article is "Antipsychotic drug efficacy correlates with the modulation of D1 rather than D2 receptor-expressing striatal projection neurons."

More information: Seongsik Yun et al, Antipsychotic drug efficacy correlates with the modulation of D1 rather than D2 receptor-expressing striatal projection neurons, *Nature Neuroscience* (2023). [DOI: 10.1038/s41593-023-01390-9](https://doi.org/10.1038/s41593-023-01390-9)

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