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A promising new class of psychotropic drugs

A newly developed drug stabilizes dopamine and serotonin levels using a novel mechanism. It effectively treats psychosis in patients with schizophrenia, and researchers are testing its efficacy for Parkinson's disease as well.

Psychotic disorders like schizophrenia are often neurodevelopmental; they affect less than one percent of the global population. But psychosis also occurs in neurodegenerative diseases such as Parkinson's disease. Although more than half of all people with Parkinson's disease experience psychotic symptoms such as hallucinations and delusions in the late stages of the disease, how psychosis develops in these patients isn't clear.

Treatments for psychosis are limited; their efficacy is inconsistent amongst patients, and they often cause serious side effects. In an effort to develop better options for patients, researchers at the pharmaceutical company Sunovion are testing a new compound, ulotaront (SEP-363856) , to treat psychosis. It proved effective enough in schizophrenia patients to earn a breakthrough therapy designation in 2019 by the FDA to speed its development.

Although initial clinical trials in patients with schizophrenia showed significant improvements in psychotic symptoms with limited adverse effects (1), the data for Parkinson's disease remains inconclusive (2). Sunovion is ramping up for larger-scale trials to further test the drug.

Psychosis in both schizophrenia and Parkinson's disease likely results from a disruption in dopamine signaling. Schizophrenia associates with overactive dopamine neurons, while patients with Parkinson's disease lose dopamine neurons over time, resulting in motor defects and psychosis.

Sunovion researchers don't completely understand how ulotaront interacts with dopamine signaling pathways, but they know that it doesn't work like other antipsychotics, which may be what gives it an edge (3).

For more than fifty years, most antipsychotic medications on the market have blocked a component of dopamine receptors known as D2. This receptor component is critical for communication between neurons, and its dysregulation can affect memory formation and cognition. D2-binding drugs have some major drawbacks. They have serious, sometimes irreversible side effects such as uncontrollable muscle movements.

In the 1980s, researchers discovered a new set of drugs that effectively treated psychosis in patients with schizophrenia. These drugs antagonized serotonin receptor 5-HT2A, the target of psychedelic drugs like LSD and a critical player in learning and memory. Although this serotonin receptor antagonist reduced the number of adverse motor effects in patients with schizophrenia, they still experienced significant weight gain, and the drug wasn't more

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effective than D2 inhibitors alone or in combination. In fact, neither drug effectively treated all of the symptoms of schizophrenia.

Scientists developed ulotaront without a specific mechanism in mind with the hope of overcoming the problems with its predecessors. In early testing, they treated mice with schizophrenia-like phenotypes with several potential drug compounds and analyzed their behavior using machine learning technology. Among the compounds tested, ulotaront was the clear winner for improving schizophrenia symptoms.

“[We] really focused on the dopamine circuit and the dysregulation of the dopamine circuit in psychosis, which is most dysregulated in schizophrenic patients who suffer from delusions or false beliefs,” said Koblan.

When they began to look for the mechanism of action, Koblan’s team discovered that ulotaront likely targets 5-HT2A and another receptor, Trace amine-associated receptor 1 (TAAR1), which acts as a receptor for multiple neurotransmitters such as dopamine, norepinephrine, and serotonin (3). Ulotaront introduces a new class of antipsychotic drugs, potentially bringing a new treatment option to patients for the first time in decades.

Last year, Sunovion researchers completed a four-week long phase II clinical trial with 240 patients, half prescribed placebo and the other half ulotaront and reported their results in the *New England Journal of Medicine*. Patients prescribed the new compound demonstrated improvement in psychosis related symptoms such as delusions. Additionally, they reported minimal side effects, which mostly presented as gastrointestinal problems such as nausea and diarrhea. Sunovion researchers are currently conducting four large-scale phase III clinical trials across multiple institutes to validate the drug’s efficacy and safety, an effort they dubbed DIAMOND (Developing Innovative Approaches for Mental Disorders).

To further explore the drug’s potential for patients with Parkinson’s disease, Sunovion recently conducted a small-scale study with approximately 30 patients experiencing Parkinson’s disease related psychosis. The results, recently published in Neurology, revealed a trending improvement in psychotic symptoms that was not significantly different from results seen in the placebo group (2). Koblan emphasized that this is a preliminary, proof of concept study; they are currently testing this drug in Parkinson’s patients in a larger phase II trial.

Patients with schizophrenia and Parkinson’s disease both suffer from hallucinations, but schizophrenia associates with auditory hallucinations, while Parkinson’s disease associates with visual hallucinations. This disparity may mean that the drug affects the two patient populations differently.

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“It appears that the dopamine pathway may be dysregulated in a differential manner in a Parkinson's patient compared to a schizophrenia patient,” said Koblan. “We are conducting nonclinical as well as early translational medicine studies in both Parkinson's patients and in schizophrenia patients to try and better understand how this novel mechanism of action of a TAAR1 agonist works.”

References:

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