Novel Drugs Targeting Different athways Show Promise in Schizophrenia

“We treat the positive symptoms very well, but those are not the ones that hold people back,” Andrew J Cutler, MD, clinical associate professor in the Department of Psychiatry and Behavioral Sciences at the Norton College of Medicine at the State University of New York Upstate Medical University in Syracuse, NY, said in a session regarding the negative symptoms of schizophrenia at the American Association of Psychiatric Pharmacists Conference 2024. In the session, Cutler highlighted potential novel therapeutics that target a variety of other mechanisms of schizophrenia.

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“Traditional postsynaptic receptor blockers are very good at treating the positive symptoms, and the newer generation of atypical antipsychotics, we have a lot of hope they might work on some of these symptoms especially well, and in some patients, they do,” Cutler said in the session. “Sometimes you can make these things worse . . . Nobody likes that dopamine sucked out of the brain.”

Cutler stated that positive symptoms of schizophrenia are symptoms that are added to a patient’s cognitive state, whereas non-positive symptoms are cognitive symptoms that are taken away. According to Cutler, the non-positive symptoms could potentially worsen with D2 receptor-blocking antipsychotics and result in poorer quality of life, worse outcomes, and worse treatment adherence.

Negative symptoms include anhedonia, alogia, affective blurting, avolition, and asociality, which tend to manifest between psychotic episodes. Cutler added that they can be part of the prodrome before full onset, which makes these symptoms important to identify.

Currently, the traditional medications for schizophrenia management are dopamine D2 modulators. Cutler said this is based on classic dopamine theories of schizophrenia, but these drugs have limitations, including the fact that they do not focus on the effect or worsening of negative symptoms and can pose a risk of motor symptoms.

There are currently several glycine transporter type 1 drugs in development. Cutler first focused on bitopertin, which underwent a few trials that yielded non-significant results. However, Cutler said the most interesting drug in development is iclepertin, developed by Boehringer Ingelheim.

“This one was really interesting because it was initially being looked at for negative symptoms, and what was found was it didn’t work strongly for negative symptoms, but [it worked] for cognition,” Cutler said in the session.

He added that the drug was studied in 4 different doses compared to the placebo, and multiple doses were superior to the placebo on various measures. Iclepertin was granted breakthrough designation by the FDA for cognitive impairment associated with schizophrenia, showing promise in an unmet need in schizophrenia treatment, according to the session.

However, there have been other developments in schizophrenia, including glutamate modulates, D-amino acid oxidase inhibitors, and phosphodiesterase inhibitors. Additionally, Cutler also discussed trace amine-associated receptor agonists. Finally, there are muscarinic M1 and M4 agonists and positive allosteric modulators, which can help to upstream the regulation of dopamine.

In the session, Cutler discussed the mechanisms of action for each target in schizophrenia, starting with M1 and M4 agonists. M4 agonists bind to the presynaptic ACh receptors, decreasing striatum activation of dopamine neurons and causing a reduction in positive symptoms. M1 agonists bind to postsynaptic M1 receptors in the frontal cortex and activate GABA interneurons. When the activation happens in 1 glutamate pathway, dopamine release is decreased and positive symptoms are reduced. However, when this happens in another glutamate pathway, dopamine release is increased, reducing negative and cognitive symptoms.

Cutler discussed multiple drugs that are being highlighted as muscarinic agonists, including emraclidine (Cerevel Therapeutics), which is currently in phase 2 trialsl; NBI-1117568 (Neurocrine Biosciences), which is also in phase 2 trials; and NBI-1117567 and NBI-1117569 (Neurocrine), which are both in phase 1 trials. Furthermore, Maplight is about to start phase 2 trials for ML-007C-MA, an M1/MA agonist that is formulated with a peripheral muscarinic antagonist. NMRA-266 from Neumora is also in phase 1 trials.

On September 26, 2024, the FDA is expected to make an approval decision regarding KarXT (Karuna Therapeutics), a combination of xanomeline and trospium. KarXT has demonstrated categorical response of 20% or greater for 59% of individuals in studies compared to 23% in the placebo; a response of 30% or greater for 38.6% of individuals compared to 11.5%; a response of 40% or greater for 24.1% of individuals compared to 8% with placebo; and a response of 50% or greater for 15.7% of individuals compared to 5.7%.

For TAAR1 receptors, the main trace amines that Cutler focused on, there has not been much development in the space, with only SEP-363856 being highlighted. Currently, the drug is in phase 3 development for schizophrenia after being proven safe and effective in a 4-week study of individuals with acute exacerbation of schizophrenia, according to the presentation.

Reference

Cutler AJ. Not So Positive: Treating the Negative and Cognitive Symptoms of Schizophrenia. American Association of Psychiatric Pharmacists Conference 2024; Orland, Florida; April 7-10, 2024.

News Source:

https://www.pharmacytimes.com/view/novel-drugs-targeting-different-pathways-show-promise-in-schizophrenia