Transcript Details

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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Developments in Schizophrenia Care: An Alternative to Dopamine Receptor Blockage

Announcer:
You're listening to *NeuroFrontiers* on ReachMD. On this episode, we'll hear from Dr. Steven Paul, who will be discussing the development of antipsychotic drugs for schizophrenia. Not only is Dr. Paul a Professor of Psychology and Neurology at Washington University School of Medicine in Saint Louis, but he's also the co-Founder and Board Chair at Seaport Therapeutics in Boston. Let's hear from him now.

Dr. Paul:
Antipsychotic drugs are a major class of drugs used to treat psychotic symptoms and these vary from disorder to disorder, but in the case of schizophrenia, we refer to these as positive symptoms. They're hallucinations and delusions. Usually, patients are hearing voices telling them bad things, and these can be quite scary and disruptive. And then delusions, generally paranoid delusions, include feelings that others are out to get them or that they're being bugged and monitored by the FBI and the CIA. They can be very peculiar, bizarre thoughts. So those are hallucinations and delusions.

Now, they also exist in other disorders. For example, they exist in Alzheimer's patients. About 40 percent will develop these behavioral symptoms characterized by psychotic symptoms. We refer to them as dementia-related psychosis. The psychotic symptoms are still delusional. There are hallucinations that occur, and they're still bizarre, but a somewhat different flavor in patients with Alzheimer's disease than in schizophrenia. But nonetheless we treat psychotic symptoms to this day with a class of drugs that was actually introduced in the United States in the early '50s. The first drug in this class was a drug called chlorpromazine, or Thorazine. That was discovered sort of accidentally, actually, as having these properties of reducing psychotic symptoms without producing massive sedation back in Europe in the early '50s and then introduced a little while later here in the US. And since that time—call it 1951 or 1952—up until very recently, all antipsychotic drugs work through the same fundamental mechanism. They block a type of dopamine receptor—dopamine being an important neurotransmitter—called a D2 dopamine receptor.

We haven't had anything new until just recently, when Karuna Therapeutics and Bristol-Myers Squibb successfully developed a drug referred to in the past as KarXT. And this drug doesn't block dopamine receptors for the first time in this 50, 60-year period of time. It actually stimulates a class of receptors that are called muscarinic acetylcholine receptors. They're a neurotransmitter receptor in the brain that is normally stimulated by a neurotransmitter called acetylcholine.

Now, the active ingredient in this medicine is the xanomeline, and it was being developed initially as a drug to improve memory cognition in people that had Alzheimer's disease. It was developed because the stimulation of these receptors had been shown previously both in preclinical and clinical studies to improve memory modestly. And very serendipitously, totally by chance, we discovered that among Alzheimer's patients who had these behavioral symptoms at baseline—hallucinations, delusions, and agitation—in a small percentage, about 30 percent in this trial, they seemed to go away within the first couple of weeks of treatment. And it was a 6-month outpatient trial. We looked at the emergence of these symptoms in patients during the course of that trial, xanomeline versus placebo, and sure enough, it prevented the emergence of these symptoms. That was the very first clue that this drug, xanomeline, and its mechanism, namely stimulating muscarinic receptors, might be beneficial to treat psychosis.

So, in short, we took this combination pill—it was a capsule—brought it back into the clinic, and we showed, first in phase I, that we could reduce these undesirable side effects. And they weren't eliminated completely, but they were greatly reduced. We then, with that data in hand, went back and did a phase II trial in people that had schizophrenia. This was a traditional inpatient, double-blind, placebo-controlled trial, and this combination worked really well in that patient population. We could reduce these symptoms. We did have some

mild-to-moderate cholinergic side effects, but no sedation or somnolence, which occurs with those other drugs; no weight gain or elevations of a hormone called prolactin, which is due to dopamine receptor blockade as well; and no extrapyramidal or Parkinsonian-like side effects. And it has really good efficacy. So that was really the start of what has turned out to be a very exciting new chapter in the treatment of psychosis.

Announcer:
That was Dr. Steven Paul discussing the evolving landscape of antipsychotic drugs for schizophrenia. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!