Transcript Details
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Schizophrenia Care: Managing Symptoms with Muscarinic Receptor Agonists

Announcer:
You're listening to *On the Frontlines of Schizophrenia* on ReachMD. On this episode, we'll hear from Dr. Steven Paul. Not only is he 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. He'll be discussing muscarinic acetylcholine receptor agonists as a potential new treatment for schizophrenia. Let's hear from Dr. Paul now.

Dr. Paul:
The potential benefits of these muscarinic receptor agonists like xanomeline trospium—KarXT—are that they have very profound effects in reducing positive symptoms, which are the psychotic symptoms such as hallucinations and delusions. They do this at least as well as the very best antipsychotics that are currently on the market that block dopamine receptors, but they do it without producing the adverse effects that are really problematic with that current standard of care right now. In other words, they do it without weight gain, extrapyramidal motor symptoms, or EPS, akathisia, or hyperprolactinemia. They do it without producing a lot of sedation. Patients who take these drugs have really slowed-down thinking because of the drug mechanism, so the real advantage right off the bat is these drugs look to be as effective in treating and controlling those positive symptoms as the very best drugs that are out there today but without that baggage.

Now, if it turns out that these drugs also treat negative symptoms and cognitive symptoms—those other two symptom domains of schizophrenia which the current standards of care don't treat at all—that would be an incredible contribution because negative and cognitive symptoms are the most disabling symptoms of the disease. You've got to control those positive symptoms, but what really keeps people disabled, unable to get jobs, and unable to develop relationships with people—all of the things that are the deficits in cognition, the deficits in executive function, and that social withdrawal—occurs as a result of these negative symptoms. So if we have a drug that treats all three symptom domains—positive, negative, and cognitive—that would be a major contribution and would benefit a lot of patients.

Now, like all drugs, xanomeline trospium, or KarXT, also has side effects. It produces some nausea and vomiting in a modest percentage of patients. The nausea and vomiting is mild to moderate. Patients generally don't stop taking their drug as a result. They dose right through it, and it goes away. There's also some risk of constipation due to the trospium, the peripheral receptor antagonist, that can occur. And so these things need to be monitored for. Generally, they respond to dosage reductions or slowing the titration over time, but the medicine, like all medicines, has its own side effects. But they're not the problematic, troublesome side effects of the standard typical or atypical antipsychotics that are on the market today and have been on the market for the last 50 or 60 years.

So there are five muscarinic receptors in the body. Most of them are in the brain, but the two that seem to be most important for the beneficial activity of this drug are the M4 receptor and the M1 receptor. Those two seem to be responsible for the beneficial effects both in reducing psychosis—those positive symptoms like hallucinations and delusions—as well as improving negative and cognitive symptoms. And we know that because in the animal studies where we have models of psychotic, negative, and even cognitive symptoms and those receptors are genetically eliminated, the drug effects are lost. The effects of xanomeline are lost. So we're pretty confident that stimulating those two receptors in the right way is the secret sauce to why this drug works.

Now, there are all kinds of other neural circuits involved that account for the behavioral benefits of these drugs. So, for example, while this drug does not directly block dopamine receptors and does block the effects of dopamine in an area of the brain called a striatum, the drug works presynaptically to tone down the release of dopamine that then acts at those receptors. So it's a kind of a fine-tuning as

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opposed to a sledgehammer with respect to reducing dopamine or dopaminergic neurotransmission in the brain that we believe accounts for the psychotic symptoms. We think that stimulation of muscarinic receptors, particularly M1 receptors and possibly M4 receptors, in areas of the brain like the hippocampus and the cortex which are involved in cognition and negative symptoms is responsible for the beneficial effects that we see with xanomeline trospium on those symptoms.

Announcer:
That was Dr. Steven Paul discussing how muscarinic acetylcholine receptor agonists might help treat patients with schizophrenia. To access this and other episodes in our series, visit *On the Frontlines of Schizophrenia* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!

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