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How Muscarinic Therapies Are Redefining Schizophrenia Care

**Announcer:**
You're listening to *NeuroFrontiers* on ReachMD. On this episode, sponsored by Bristol Myers Squibb, we'll hear from Dr. Michael Halassa, who's the Director of Translational Research and a Professor in the Department of Neuroscience as well as a Professor in the Department of Psychiatry at Tufts University School of Medicine in Boston. He'll be discussing a recently published consensus panel report he co-authored in the *Journal of Clinical Psychiatry* that focused on the real-world implementation of xanomeline-trospium, or XT for short, in schizophrenia care. Here's Dr. Halassa now.

**Dr. Halassa:**
Traditionally, antipsychotics have all been derived from chlorpromazine, a dopaminergic agent that blocks dopamine D2 receptors in the brain. Those are highly enriched in the basal ganglia, and blocking them is thought to reduce a hyperdopaminergic state in the brain that underlies things like positive symptoms—hearing voices or having unusual beliefs. And in line with that idea, traditional antipsychotics are efficacious when targeting these symptoms.

The new class of medications—the muscarinic agents, with XT being the first in class—are different because they target acetylcholine receptors—the M1 and M4 receptors—and those reduce the hyperdopaminergic state without blocking dopamine receptors. So therefore, their impact on motor symptoms, tremors, and dyskinesias is less or non-existent. But on top of that, they address abnormalities in the schizophrenia brain that are outside of the hyperdopaminergic state, which include things like frontal cortical deficits that underlie negative and cognitive symptoms.

When should we be considering XT in clinical practice? My view on that has been evolving over time. Initially, I used it as adjunctive treatment when traditional antipsychotic management was insufficient. That has worked quite well, and it actually had a dose-sparing effect, meaning that as we increased the muscarinic dosage, we were able to reduce the dose of traditional antipsychotics. That's an important thing because dopamine-targeting agents have many undesirable side effects. Where the muscarinics shine is in their very favorable side effect profile. They do not cause weight gain. They do not cause metabolic side effects. They do not cause motor symptoms.

As time has gone by and as we've seen the favorable side effect profile, I think that it is imperative for us to protect our patients from the negative side effects of traditional antipsychotics if we can. There will be a subset of patients that will always require dopamine agents to control their positive symptoms. But there may exist a subset of patients that are just fine on XT monotherapy or other muscarinics as they get developed in the future. The hope is that the research we are doing right now will allow us to predict these things better—to tell who's who and to target the medications or combinations of medications to people appropriately.

Now, what are the real-world effects of XT? The most obvious thing is the awakening phenotype. In a subset of people who are treated with this medication, it's almost like a light bulb switched on and they are now able to interact with the world in a way that they were not able to prior to starting the medication. The first time I saw it in one of my patients, it was absolutely remarkable. It was an older lady that I had not been able to interact with; she went from being aggressive to somebody who I would look at and I would see, 'wow, this looks like my grandmother.'

And I have seen things like that in many people that we've administered XT to, where they go from what we would think is their baseline to a state in which they are much more socially available or socially connected. That bodes well, I think, for restoring function in a subset of individuals that we have been trying to keep safe and calm down their positive symptoms.

**Announcer:**


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