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Muscarinic Cholinergic M1/M4 Stimulation: What Is the Role of Muscarinic Agents for the Treatment of Schizophrenia?

Announcer:
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Dr. Meyer:
This is Dr. Jonathan Meyer, Voluntary Clinical Professor of Psychiatry at the University of California, San Diego, here to talk about Muscarinic Cholinergic M1/M4 Stimulation: What is the Role of Muscarinic Agents for the Treatment of Schizophrenia?

For many of you, this may be a novel concept, but it was really a novel concept in the history of psychiatry, and no one thought of these mechanisms until over 30 years ago, when the folks at Eli Lilly had synthesized an M1/M4 agonist. And actually, were studying it for Alzheimer's disease. They thought, well, we'll improve cholinergic neurotransmission and improve cognition. But what they found was in fact that it also improved psychosis. And this was very exciting. This was the crack in the edifice of dopamine antagonism as the most important mechanism to treat psychosis. Based on that, people characterized the compound, they realized, well, maybe it relates to the fact that it really is a strong agonist at M1 and M4, but they didn't understand why this made it an antipsychotic.

That being said, some people took this compound and then later on gave it to schizophrenia patients just to see if we could replicate that antipsychotic effect. It was a small pilot study that clearly showed that xanomeline, as it came to be called, was effective for the treatment of schizophrenia, it improved positive symptoms, and also seemed to improve cognition as well. The big issue with it, as you can see in Table 4, is that while the compound was better tolerated in schizophrenia patients than it was in Alzheimer's patients, still significant issues with cholinergic agonism, especially vomiting.

Well, while people kind of mulled over what to do with this, they started to characterize the compound and how it actually work to make schizophrenia better. And they recognized it has two mechanisms of action. The first one was M4 agonism. We actually have cholinergic stimulation of what we call in the mouse the mesolimbic pathway. M4 actually has an auto receptor. So by giving an M4 agonist, we actually reduce cholinergic stimulation of VTA dopamine release in the mesolimbic pathway. And again, it's selective in that area associated with psychosis. We don't affect cholinergic or dopaminergic neurotransmission in the motor system, so a selective effect on those pathways associated with the positive symptoms of schizophrenia.

Also, the M1 agonism acts by a different pathway. Up in the prefrontal cortex we have GABAergic interneurons with M1 receptors. If we stimulate those, we actually have negative feedback inhibition on glutamate and its effects on dopamine release again, in the mesolimbic pathway. So we get a combination of effects, a bottom-up, and a top-down strategy, which reduce dopamine release selectively in those areas of the striatum associated with psychosis.

Before proceeding with further trials, we had to solve the problem of cholinergic agonism in the periphery. We couldn't give somebody a centrally-acting anticholinergic because that would interfere with a mechanism of action in the brain. Some smart people recognized that we have an old medicine called trospium, which is used for overactive bladder, but it does not cross the blood brain barrier. And they

combined xanomeline with trospium, it really mitigated the peripheral adverse effects without impacting the central effects, and its antipsychotic activity. And then we could proceed with clinical trials.

So there was a phase 2 study published in the *New England Journal of Medicine* in 2021, double-blind, inpatient trial that adults with an acute exacerbation of schizophrenia. And 91%, were able to tolerate a titration to the highest dose of xanomeline/trospium. And look at that effect size, 0.75. This is larger than anything we've seen in a long time in schizophrenia. Most of our drugs have effect sizes between 0.4 and maybe 0.6. Also, we saw tolerability, as I mentioned, which was quite good. Discontinuation, as you can see, numerical was almost exactly the same as placebo. We didn't see significant changes on weight. And if you look at the cholinergic, both anti and pro, there were numerical differences, but these were mostly transient, and not a cause of dropout. So people experienced them, and they didn't notice them during the titration. But as we see by the discontinuation rate, they weren't significant enough to cause dropout.

Also, we now have a phase 3 study with a very similar effect size, 0.61. Again, and this is as large as we've seen for decades in schizophrenia, probably because placebo response has gotten so much better. This is very exciting news that this really is a promising effective medication with a unique mechanism of action, one which is not only selective in those areas of the striatum associated with psychosis, but most importantly, maybe even a slightly more effective than things we've had for the last 30 years. We look at the dropout rates, again, very, very similar to placebo. Negative symptoms, also we're showing benefit on. Maybe not as robust as total symptoms, but still an effective drug overall for symptom reduction in schizophrenia.

Because of the excitement from the discovery and data on xanomeline, people are looking at other both M1 and M4 strategies. In some instances, these are not agonists but what are called positive allosteric modulators, which just facilitate neurotransmission across that specific receptor subtype. These are still in earlier phase studies, but I think most importantly, we recognize that these are robust, effective mechanisms. And again, another revolution in the treatment of schizophrenia.

So in summary, we've now come to realize that we can make schizophrenia better with drugs that don't bind to D2 receptors. And in this case, we have compounds which facilitate or stimulate M1 or M4 receptor activity, which will really be important for the treatment of schizophrenia across a broad spectrum of patients without the motoric, endocrine, or metabolic adverse effects we've seen with older agents.

This is Dr. Jonathan Meyer. Thank you so much for listening to this episode.

Announcer:
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