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TAAR1: What Is the Role of TAAR1 Agonism 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, talking about TAAR1: and What is the Role of TAAR1 Agonism for the Treatment of Schizophrenia?

Well, if you have no idea what I'm talking about TAAR1 refers to a receptor, specifically for trace amines. These are chemicals which look very similar to traditional monoamine neurotransmitters, expressed though at much lower levels. And also, the receptors are predominantly intracellular.

In this complex family of receptors, there's one which has emerged as a risk issue for schizophrenia, which is TAAR1. When people started synthesizing agonists as well as mouse models about a decade ago, and those mouse models have been very instructive. So these are what are called knockouts. They don't express a TAAR1 receptor, so you can consider them having essentially 100% antagonism. A couple of things: in their basal state, they look normal, maybe similar to wild-type mice, but when you give them a dopamine challenge, such as an amphetamine, they have enhanced response. What's interesting is that they tend to have more dopamine overactivity in the area of their striatum associated with psychosis, but not so much in the motor area. And that has implications for treatment. We don't see problems with dopamine transporter function. So really, what we're seeing is a lot of presynaptic dopamine release in areas which look like the areas in the human brain associated with psychosis. And not surprisingly, when you look at the human brain, you see that TAAR1 receptors are expressed in those key regions, which we feel like are important symptoms for schizophrenia, especially in the striatum, and also in the cortex as well.

So the question is, if I give a TAAR1 agonist to a human being, what happens? Well, what we think is primarily what we're doing is moderating presynaptic dopamine release, which improves positive symptoms. And importantly, we do it selectively in those areas associated with psychosis in the striatum, but not in the motor areas. So the whole concept is that we have not only something which reduces presynaptic dopamine release, but it does it selectively. And that is really a novel finding for any psychotropic that we can selectively affect dopamine neurotransmission, make psychosis better, but maybe not have motor adverse effects.

The one compound which is furthest along in clinical development is ulotaront, which is a TAAR1 agonist, which also has some serotonin-1A properties. The serotonin-1A, we don't think makes this drug an antipsychotic, it's the TAAR1 agonism, but may help with other aspects of the molecule. Most importantly, it does not have D2 blockade, it seems to, in preclinical models, do all the things we want from an antipsychotic, but most importantly, it does not appear to have motoric adverse effects.

Well, people always want to say, well, that's fine and good, but I'm not treating mice, I'm treating human beings. Is there human data? And here it is. We have a pivotal phase 2B trial 4-week, double-blind, inpatient study with a placebo control, as well as a 26-week open-label extension. Most importantly, it really does work as an antipsychotic, you can see separation by week 4, the effect size is very

much in line with other antipsychotics with a number needed to treat of 5. But remember this effect size, this is for total symptom reduction, 0.45. Usually we're not as good at reducing negative symptoms as overall symptoms. But what's interesting about ulotaront is the effect size for negative symptom reduction is the same as total symptoms. This is really a novel finding, and one which we hope will be replicated in the phase 3 trials.

Most importantly, we want any novel compound or any treatment for schizophrenia to be tolerable. So here's a list of the adverse events occurring in the pivotal 4-week double-blind placebo-controlled trial that occurred in 2% or more of the ulotaront group and greater than placebo. One thing you don't see in this table are EPS-related events. That speaks to what I talked about before, which was the selectivity of the mechanism. We also see very, very similar numbers across many of these adverse events which may be numerically greater than placebo. But if you look at the numbers needed to harm, they are quite large. But more specifically, if we look at metabolics, we also don't see clinically significant effects or in endocrine adverse effects as well. This is really important. We want our treatments to be tolerable as well as effective. And we seem to have done both with these TAAR1 agonists.

In summary, TAAR1 agonism is really an exciting new strategy for the treatment of schizophrenia. It does not bind to D2 receptors, it appears to reduce positive symptoms without incurring motor adverse effects. For ulotaront, we see data showing significant reduction in negative symptoms, and most importantly, without metabolic endocrine adverse effects or motor adverse effects. We really are looking at a revolution in the treatment of schizophrenia. And I think we're very excited to see what the future holds for TAAR1 agonism.

This is Dr. Jonathan Meyer. Thank you for watching this episode.

Announcer:
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