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Emerging From the Darkness to the Light: A New Day Is Dawning in the Discovery of Novel Treatment Targets for SCZ

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Dr. Correll:
Welcome everyone to the program titled Emerging From the Darkness to the Light: A New Day is Dawning in the Discovery of Novel Treatment Targets for Schizophrenia. My name is Christoph Correll. I'm Professor of Psychiatry and Molecular Medicine at the Zucker School of Medicine at Hofstra Northwell. And I'm joined by my two colleagues and friends, Jonathan Meyer and Les Citrome, who will now introduce themselves. Jonathan.

Dr. Meyer:
Hi, I'm Jonathan Meyer. I'm a Voluntary Clinical Professor of Psychiatry at the University of California, San Diego.

Dr. Citrome:
And I'm Leslie Citrome. I'm a psychiatrist based north of New York City, and I'm Clinical Professor of Psychiatry and Behavioral Sciences at New York Medical College in Valhalla, New York.

Dr. Correll:
Excellent. Now, I'm really pleased to work with the two of you on this because we're all so eagerly awaiting new developments in treatment of schizophrenia. Jonathan, do you want to start us off with something that's called TAAR1? What's that?

Dr. Meyer:
So TAAR1 really refers to trace amine-associated receptors. So trace amines are compounds with structure look very similar to the classical monoamines, like norepinephrine or dopamine. But these trace amines, things like beta phenylethylamine and octopamine, are present in much lower levels. And the receptors tend to be intracellular. So they're much harder to discover and characterize, and both understand. But we've appreciated over the past 20 years that there's something that they do, which modulates a lot of monoaminergic activity. And some exciting new pathways and discovery allowed us to generate a compound from preclinical discovery that TAAR1 in particular, is a receptor that moderates dopaminergic activity. What's exciting about this is that it does it without binding to D2 receptors. And that's really part of the revolution, the emergence from the shadow of D2 blockade, and all the clinical implications. TAAR1 agonists, in particular, we think help moderate presynaptic dopamine release. And as you know, Christoph, the imaging studies show that in human beings, if you have positive symptoms of psychosis, it's due to excessive presynaptic dopamine release in a certain part of the striatum. Now, if you're a rat, we'll call that the striatum, that part, the mesolimbic pathway. In humans, it's a slightly different pathway, but the same concept. Well, we solved that problem with D2 blockade, but TAAR1 agonists actually decrease presynaptic dopamine release, and they have very limited effects in the motor pathway. So we have selectivity, or presynaptic dopamine release, without binding to D2 receptors.

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And really what's exciting, Christoph, is that we now have phase 2B data, which showed significant effects of TAAR1 agonists in patients who were adults with an acute exacerbation of schizophrenia, without motoric effects, without orthostasis, without significant sedation, and without significant metabolic effects. So it's everything we've wanted in a compound for schizophrenia, and possibly with some unique additional benefits on negative symptoms.

Dr. Correll:
So let me get this right. So trace amines basically are not our usual neurotransmitters that are released from a synapse, they're inside these receptors inside the synapse. And then what happens is, when TAAR1 binds to it, or an agonist binds to it, then there is a decrease in presynaptic dopamine. But there's also something that happens at the postsynaptic dopamine receptor, correct? Heterodimerization, what's that?

Dr. Meyer:
Well, heterodimerization actually happens both pre and postsynaptically. So this TAAR1 intracellular receptor, when it gets activated, it actually migrates to the cell membrane where it gloms onto the D2 receptor. And that's how we think it moderates a lot of the dopaminergic activity. Presynaptically, what we know it does is it actually increases the sensitivity of the auto receptor to feedback inhibition. So we think that's a big part of decreasing presynaptic dopamine release. Postsynaptically, it also seems to moderate the dopamine signal, so any of the dopamine that's released and goes across the synapse, doesn't have the same impact. The net effect, again, is reduction in positive symptoms.

But I'll just close on this. Preclinical models and also clinical data show a lot of interesting activities for TAAR1 agonists. I mentioned the human data about benefits on negative symptoms. Animal models also showed benefits on mood maybe related to TAAR1 glomming on or moderating serotonin release, and also both cognitive and even metabolic benefits too. So very exciting agents and we're just waiting for phase 3 data to see how they play out and maybe be of value to our patients with schizophrenia.

Dr. Correll:
Excellent. Thanks very much, Jonathan. So that seems to be a totally new class of medications that was recognized by the WHO, because it's called ulotaront, so the TAAR mechanism is in there. And we're waiting for at least one more positive study and hopefully no negative side effects signals.

But, Les, you're going to talk about another very exciting area. And that has to do with muscarinic receptors. What is that about?

Dr. Citrome:
So this is actually old fashioned receptors that we've known about for quite some time, in contrast to trace amine receptors. So the muscarinic cholinergic hypothesis of schizophrenia has been around for a while, and pro-cholinergic drugs were observed to increase lucid intervals in people with psychosis in the 1950s, but not well tolerated. And further development was actually abandoned until actually quite recently.

We know that cholinergic systems directly modulate striatal dopaminergic function. So we think in humans, it's in the associative striatum. In animal models, it's going to be in the ventral striatum, but in part of the striatum, we can modulate dopaminergic function upstream through cholinergic systems. And we also know that cholinergic systems directly regulate descending glutamate pathways that interact with striatal dopamine circuits.

There's a couple of ways of decreasing dopamine signaling, thus, decreasing hallucinations and delusions without touching the postsynaptic D2 receptor in the striatum. So this, like TAAR1, that whole business, we can actually treat psychosis without directly binding to postsynaptic D2 receptors. So this is a revolution.

Now, what are these muscarinic receptors? Well, in the brain is M1 and M4, are the targets. And they're expressed, actually, less so in people with schizophrenia than in people without schizophrenia. And there's also some animal models that have examined this, There is a muscarinic cholinergic agonist called xanomeline, and it's an - it focuses on M1 and M4 in the brain. However, it also binds to muscarinic receptors outside the brain in the periphery, leading to side effects. So xanomeline was noted to have antipsychotic properties, it just wasn't well tolerated because of peripheral side effects.

So someone thought of again, of maybe if we can add an antimuscarinic agent together with the xanomeline, maybe we'd have a more tolerable agent that will work in people with schizophrenia. So these - the receptors, the muscarinic receptors in play here are M2/M3. They're the major peripheral subtypes that underlie the dose-limiting GI side effects principally. And by adding trospium, a muscarinic receptor antagonist to xanomeline, we have the secret sauce of treating psychosis and moderating the otherwise intolerable side effects peripherally. Now, trospium itself does not cross the blood-brain barrier. So it'll act as a peripheral antagonist and do its magic, so to speak, in making xanomeline more tolerable. Now, this was all very interesting. It’s not exactly new, this was figured out in the 1950s. But the actual technology of making this possible only was available now.

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And we have a clinical trial. And that was in phase 2 that was published in the *New England Journal of Medicine* that demonstrated acute antipsychotic efficacy in people with schizophrenia in a 5-week period with xanomeline/trospium combination administered BID. So that was pretty interesting, that you can treat schizophrenia without blocking postsynaptic D2 receptors through this mechanism. It was reasonably well tolerated. There was no, you know, the whole thing about waking and prolactin increase and drug-induced motor movements, they were not present. So we have another way of treating schizophrenia that doesn't lead to those same side effects that we've been saddled with for the past 70 years.

Now, the effect size and the reduction of these symptoms was actually quite respectable, and looks better in my eyes than some of the other products that we have today. So that remains to be seen how it translates into the real world. But I'm encouraged because there's more than one study now. There are two additional studies, they're in phase 3 - they were phase 3 studies. The reports have been out, one in a poster and the other in a press release. I think we're going to see a poster of it pretty soon, showing the exact same thing as that first phase 2 trial as published in the *New England Journal of Medicine*. So three studies. All that we're waiting on now is some longer-term tolerability and safety data that extends out to a year. And I think they're good to go in terms of submission to the FDA for approval in the not-too-distant future.

So I'm excited about this way of treating schizophrenia, avoiding the postsynaptic D2 receptors is a high priority for me, because I don't want to deal with those problems of motoric adverse events or eventual tardive dyskinesia risk, and all of that.

Dr. Correll:
Well, thanks very much for this great summary about xanomeline and trospium. So it's an M1/M4 agonist. And basically, the M4 reduces cholinergic output in the ventral tegmental area, and also in the striatum, thereby reducing dopamine tone. And the M1 coming down, actually stimulates GABA, the brake in the system, which then decreases glutamate, as you said, which then decreases dopamine. And that's basically a dual approach. And maybe the M1 could also have additional features for cognition or negative symptoms. So this is really exciting. And we have three positive trials. There's maybe in the last 30 seconds, another agent in the same bucket in a way that we're also excited about

Dr. Citrome:
Emraclidine. So that focuses on M4, the M4 muscarinic receptor. So it doesn't have any M1 activity, but M4 may be sufficient. And there was a study, a preliminary study, that shows a good signal there, and we're waiting for additional data.

Dr. Correll:
And it's actually not an agonist like hitting the receptor and simulating it's a positive allosteric modulator, enhancing the signaling indirectly, which is also exciting that that also seems to work.

Well, Jonathan, Les, thank you so much for this great summary that hopefully will also elucidate some of these mechanisms to our audience. And in the next section, we will also talk about the application of these potential new treatments. Thank you.

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