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Novel Agents Are Emerging From the Therapeutic Shadows of Post-Synaptic Dopamine Modulation: What Are the Benefits and Where Will These New Agents Fit Within the Treatment Paradigm?

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Dr. Correll:
Hello everyone. Welcome to the program titled Novel Agents are Emerging from the Therapeutic Shadows of Post-Synaptic Dopamine Modulation: What are the Benefits and Where Will These New Agents Fit Within the Treatment Paradigm? My name is Christoph Correll. I am Professor of Psychiatry at the Zucker School of Medicine at Hofstra Northwell. And I'm joined by my colleagues and friends, Jonathan Meyer and Leslie Citrome, who will now introduce themselves.

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

Dr. Citrome:
I'm Leslie Citrome. I'm a psychiatrist based just 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:
Great, thanks for joining me in discussing the potential application of novel mechanisms of action to the treatment of schizophrenia. And let's just review this briefly. We've been waiting for this for 7, 7 decades. Basically, we've had postsynaptic dopamine modulation since the 1950s. And it's not for lack of trying, there hasn't been much that really came through. But now what happened in the last 5 years or so maybe beats what happened in the last 30 or 50 years in terms of innovation. That is not just a theory, but we now have data that is really exciting. And we reviewed that in a prior episode. And we'll focus today on the potential application of a TAAR1 agonist called ulotaront, and that doesn't have postsynaptic binding or to dopamine receptors and the muscarinic agonist, xanomeline and trospium, combination, which is an M1/M4 agonist also doesn't bind to postsynaptic receptors on the dopamine system, so no EPS, no akathisia, no tardive dyskinesia risk, prolactin isn't decreased. These agents also didn't have sedation or weight gain. So safety seems to be pretty good. But what about efficacy and sequencing of treatment? So who wants to go first? Where would these treatments actually fit in our paradigm? Modal therapy, adjunctive, which patient population?

Dr. Citrome:
Actually, I'll take a stab at it. I've been waiting with bated breath for something like this, because I am simply tired of having to explain all the downsides down to antipsychotics to my patients. ‘And if I can offer something that, you know, you may have heard about this drug or this other drug, and you may have your friend on it, and so on, this is completely different. And you know what, it may work better for you.’ So that that's actually my hope, that this will not only be better tolerated, but actually work better, at least for some of my patients.

And, you know, this is not unrealistic. We know that when we treat hypertension, there are different antihypertensives available and they work differently. So why not schizophrenia? And perhaps someone who is not going to respond all that well to one type of medication may respond better to another. It's just that up to now, we haven't had anything else to offer. They've all been, you know, basically dopamine receptor antagonists or partial agonists. And they're pretty much very similar. So that's my hope. And maybe it'll work better for some.

Dr. Correll:
Jonathan?

Dr. Meyer:
Yeah, so I'll only add one thought on to what Les said is that xanomeline/trospium has been studied not only as monotherapy with tremendous effect sizes, as was alluded to, but also adjunctively as well. And that's really a very interesting concept that something has actually been studied adjunctively, works by a presynaptic mechanism which may be complementary to the postsynaptic blockade. And the only unique aspect about muscarinic agonists is they won't play well with muscarinic antagonists. So I know, Les and Christoph, you've been talking for years about trying to get people off of benztropine and anticholinergics for its cognitive problems. Well, here's another reason: they're going to interfere with the mechanism of action of a cholinergic agonist. So that's just something we have to think about as a practical strategy of implementation.

The ulotaront TAAR1 agonists actually don't have that issue. The preclinical models show that you could add a TAAR1 agonist onto existing antipsychotic treatment and improve the efficacy of an existing antipsychotic, again without adding on motoric adverse effects. And what's most interesting is, at least in animal models, it actually helps reverse some of the metabolic problems that you get from a drug like olanzapine. Whether that translates into humans, we don't know. But what we can say from the monotherapy study of ulotaront in adults with schizophrenia is that we don't see motoric adverse effects. We don't see metabolic adverse effects. We don't see prolactin adverse effects. But maybe a unique signal for a bit more selective benefit on negative symptoms that we've had with dopamine modulators.

So where would you place this? I think we've recognized especially you, Christoph, as a child psychiatrist, early intolerability predicts nonadherence. And we've always wanted agents which didn't have the endocrine, metabolic, and D2 related adverse effects. And I think for many of us who work with first-episode psychosis patients, getting to these agents as early as possible may be beneficial in a lot of ways, not only efficacy, but also tolerability, and the tolerability linked to adherence.

Dr. Citrome:
You know, in my career, I've spent the bulk of it on people who are chronically mentally ill, you know, 40 50, 60 years old, and we're no strangers to polypharmacy with this population. Up to now, the polypharmacy has been, you know, combining things that are relatively similar. Well, we can leverage some things, like we can reduce prolactin by adding a partial agonist, but basically, we're kind of stuck. And having different mechanism of action, different drugs that are utterly different, maybe we have a shot at synergy here, or at least an additive effect. So you know, it's nice to have one plus one equals three, I'll be happy with one plus one equals two, if we can get it. The cardiologists have it, why can't us?

Dr. Correll:
So it seems to me we have novel mechanisms of action, and there are different scenarios. It could be basically just another road to discover a decrease of dopamine helping psychosis, and it's somewhat on an even keel. It could be for patients who are not responding well to the postsynaptic dopamine modulation, and by having now the selective additional or sole presynaptic modulation, you help those that can't be helped or have only partial response, either in monotherapy, or in combination treatment. It could be that even the treatment-resistant patients could be now helped closely to what we see with clozapine, which also has muscarinic agonism, for example. We don't know that yet. It could be that there's a selective improvement of negative or cognitive symptoms, which would also steer us to certain patients, or even precision psychiatry, people who have a somehow derangement in the TAAR1 system or in the muscarinic system are the champions of these treatments. Obviously, we will only find out once these treatments get into our hands, but it's very exciting that we have antipsychotic efficacy without postsynaptic dopamine blockade and without the side effects that come with that type of medication. There can be different side effects like in the muscarinic agonist, TAAR1, but less so - but the M1 agonism needs to be countered, the pro-cholinergic side effects, gastrointestinal ones, nausea, vomiting, and then if you give an anticholinergic that's peripheral, and you'll get some dry mouth and constipation, but again, that might be a little price to pay for improved efficacy in some patients.

So thanks very much for summarizing this for us. And this is just the beginning of discussing it because we need to get it into our hands and also have shared decision-making with patients in order to see whether it's journey leads us, but it's an exciting journey right now.

So thanks very much, Les and Jonathan, and look forward to discussing this further in the future.

Announcer:
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