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The Role of TAAR1 in Treating Neuropsychiatric Disorders

Announcer:
You're listening to *NeuroFrontier's* on ReachMD, and this episode is supported by Sunovion Pharmaceuticals Inc. and Otsuka Pharmaceutical Co. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and joining me to examine the role of TAAR1 and its application in the treatment of neuropsychiatric disorders is Dr. Craig Chepke, who's the Medical Director of Excel Psychiatric Associates and Clinical Assistant Professor of Psychiatry at SUNY Upstate Medical University. Dr. Chepke, thank you for being here today.

Dr. Chepke:
Thank you so much for having me today. I'm excited to be here.

Dr. Turck:
To start us off, Dr. Chepke, would you give us some background on what TAAR1 is?

Dr. Chepke:
Sure. So to break down the acronym, it stands for trace amine-associated receptor, and it's type 1. And so to start off, just what are trace amines? So trace amines are structurally similar to the monoamines that we all are familiar with, things like serotonin, dopamine, and norepinephrine. So chemically, they look a lot like those molecules. But they, as the name implies, are only found in the body in trace amounts. So we've known about trace amines for 100 years or more, but they were thought to be just kind of incidental trash or metabolites that the body might have produced and didn't really serve any biological function.

But then, we found receptors for these trace amines, and then that made it a neurotransmitter. So that's a big deal. And there are a couple of dozen overall trace amine receptors. The human body only expresses several of them. And what we think is most important for neuropsychiatric illnesses is the TAAR1 receptor. So that's an emerging potential class of medications that could have wide-ranging benefits hopefully, if trials pan out, for people with multiple different neuropsychiatric illnesses.

Dr. Turck:
And with that in mind, what are the benefits of TAAR1 agonists?

Dr. Chepke:
So that's a great question. In terms of the benefits of TAAR1 agonists, we're going to have to focus a lot on the preclinical evidence. Because clinical evidence from human studies is still very early, we only have one completed phase 2 study of one TAAR1 agonist in schizophrenia. And then there are a number of phase 3 programs that are currently running, for which we don't have results. There's other phase 2 programs for other molecules, but we have very little human data so far, although what we have is promising.

In terms of preclinically, there's a pretty wide variety of different things that we've seen with TAAR1 agonists. So for instance, there's anti-psychotic effects that have been seen, anti-depressant effects, anxiolytic effects, and even the TAAR1 agonists in preclinical models have reduced the weight gain associated with administration of olanzapine. So when you co-administer olanzapine with a TAAR1 agonist, there's not the weight gain seen with olanzapine monotherapy. So that's a really broad range. It lets me know that we're just really scratching the surface of what TAAR1 agonist can do.

Dr. Turck:
Now you've started to touch on this already, but where might TAAR1 agonists play a role in neuropsychiatric disorder treatment

paradigms?

Dr. Chepke:
Yeah, so I mentioned that there could be a wide range of different applications, but where it's starting is with schizophrenia. Given that there's some pretty good data preclinically, there's a reduction in the amount of dopamine transmission in the ventral tegmental area that in the mouse striatum are associated with psychosis, then that's where it's starting. And there has been, as I said, a successful phase 2 study of ulotaront in schizophrenia, and it's being looked at in phase 3. So that's the first place, but it's not going to stop there.

As I mentioned, there are potential mood effects and antidepressant effects. And there's also a study that's just in the planning stages for use of ulotaront, once again, for adjunct treatment of major depressive disorder. And there could be potentially wide-ranging others. There's another molecule that's actually currently on the market, solriamfetol, which is a medication approved for excessive daytime sleepiness associated with sleep apnea and narcolepsy, and it was recently shown that it has TAAR1 agonist effects, as well.

Dr. Turck:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Craig Chepke about the use of TAAR1 agonists in treating neuropsychiatric disorders.

So, Dr. Chepke, I was wondering if you could go into a little bit more detail about how TAAR1 activity plays a role in reducing symptoms in patients with schizophrenia or psychosis?

Dr. Chepke:
Sure, so you know, we've had medications for schizophrenia for 70 plus years since chlorpromazine, but they've all revolved more or less around the D2 receptor; assured all antipsychotics have more receptor binding effects than just at the D2 receptor. But they all bind directly in some way, shape, or form to some degree to the D2 receptor. And schizophrenia being such a heterogeneous illness, both syndromically, but also likely genetically and etiologically, in ways we don't understand, that there's no way we're ever going to get the treatment effects that we need for every person with schizophrenia with just really focusing in as the centerpiece on that one receptor.

So, there's a saying that all roads lead to Rome. And with the psychosis symptoms of schizophrenia, certainly, all roads kind of lead to dopamine. That there is a really important dopamine effect, but it might just be that the D2 receptor directly binding it, either antagonizing it or partial agonizing it, could have with all of our treatment options, have some baggage associated with it. There's some issues with it. So we want to modulate dopamine but maybe not directly by direct D2 binding.

So what TAAR1 agonists do is that they promote something called heterodimerization. So hetero meaning two different, so the TAAR1 agonist induces the TAAR1 receptor to form a heterodimer with the D2 receptor. So they joined forces, and the power of both together seems to be better than just the one alone.

And as I mentioned a couple of minutes ago, presynaptically, it increases the sensitivity of the D2 receptor. The presynaptic D2 receptor acts kind of like a circuit breaker. When it detects dopamine in the synapse, it says 'well wait a minute, we've got plenty of dopamine here, no need to synthesize more, no need to release that much more.' So we're going to shut it down, we're going to pull the plug, and not release more dopamine. And then postsynaptically, there's some problems there as well, that when the dopamine binds postsynaptically, certain pathways in the second messenger downstream system can be overactivated and contribute to that psychosis. The heterodimerization there of the TAAR1 receptor with the D2 receptor, again, facilitated by the TAAR1 agonist, will shift the intracellular signaling away from those pathways more associated with psychosis towards ones that are not as associated with psychosis. So it's working on both sides of the synapse, which is really interesting, and could maybe have some potentially important benefits.

Dr. Turck:
So as we wrap up our discussion, Dr. Chepke, are there any final insights you would like to leave with our audience today?

Dr. Chepke:
Well, I always like to leave on a measure of hope. I think the most important thing a clinician can give to a patient is not a prescription but hope. Hope and education, maybe I should say two things. But I think this really should inspire some hope in the minds of the listeners out there. Because honestly, we don't have great outcomes with treating schizophrenia. Despite the dozens of different molecules that we have, and then different formulations of each molecule, in some cases long-acting injectables, patches, oral, or dissolving. There's many different ways that we've tried to treat schizophrenia, with only limited success in a limited subset of patients. And so having completely different mechanisms gives me tremendous hope that if these later phase trials do pan out, as I think all of us are hoping that they will, that we could really start to see some benefits in people who have not seen benefit with the current armamentarium. And that hopefully should give us all hope that we can get better outcomes for people living with schizophrenia.

Dr. Turck:
Well with those final thoughts in mind, I want to thank my guest, Dr. Craig Chepke, for joining me to discuss TAAR1 and its role in the treatment of neuropsychiatric disorders. Dr. Chepke, it was great having you on the program.

Dr. Chepke:
It was great to be here. Thanks so much for bringing me on.

Announcer:
This episode of *NeuroFrontier's* was sponsored by Sunovion Otsuka Alliance. To access this and other episodes in this series, visit ReachMD.com/Neuro Frontiers, where you can Be Part of the Knowledge. Thanks for listening!