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Psych Congress 2022: A Look at New Mechanisms of Action in Schizophrenia

Dr. Turck:
Welcome to the *Psych Congress Action Center* on ReachMD. I'm Dr. Charles Turck, and joining me is Dr. Craig Chepke, who is the Medical Director of Excel Psychiatric Associates and a member of the Psych Congress Steering Committee. One of Dr. Chepke's sessions at the 2022 Psych Congress focuses on the new mechanisms of action for schizophrenia treatments, which is what we'll be talking about today.

Dr. Chepke, welcome to the program.

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

Dr. Turck:
Now, Dr. Chepke, although we've made some progress in the treatment of schizophrenia, unmet needs still remain. So what are some areas that are lacking in terms of treatment options?

Dr. Chepke:
Well, unfortunately, there's quite a few unmet needs, honestly. Ever since the first antipsychotic was discovered, chlorpromazine, there's been, as you said, some progress but really honestly not that much. If you look at the efficacy of the antipsychotics in the 70-some years since chlorpromazine, they are all relatively comparable in terms of efficacy. And furthermore, the efficacy that we're talking about is generally mostly in the positive symptom domain. The other core symptoms in clusters of schizophrenia, namely the negative symptoms and the cognitive dysfunction that are absolutely critical tellers, and in many cases the greater predictor of disability over the lifespan for someone with schizophrenia rather than the positive symptoms, those are not well-addressed by really any of the current treatments. We have made some progress in terms of tolerability, but still tolerability issues remain, things like motor side effects: akathisia, dystonia, tardive dyskinesia; metabolic side effects, such as weight gain, dyslipidemia, and so on. So unfortunately, I think we do have a lot of ways that we could improve the current state of the art of the schizophrenia treatment.

Dr. Turck:
And with that background in mind, let's zero in on your Psych Congress session focusing on emerging therapies in schizophrenia, one of them being TAAR1 agonists. Would you explain what a TAAR1 agonist is and how it might work as a potential treatment option for schizophrenia?

Dr. Chepke:
You bet. I would love to because I think this is a really cool mechanism of action. So historically, we've discovered in psychiatry our new medications by serendipity in the many decades past, just happening to notice that a medication given for some other purpose had

some psychiatric potential benefits, and then in the past several decades, it's been more by what we call rational design. A very skilled chemist would take the chemical structures of the known antipsychotics and then deliberately tweak them in specific ways to try and dial up the activity of certain receptors we believed were beneficial, so increasing the levels of serotonin 2A antagonism or increasing the serotonin 1A partial agonism, decreasing the anticholinergic, antimuscarinic antagonism, things like that. But like I said earlier, the efficacy has really plateaued, and so we needed a different approach; so one company took a novel idea, which is using a combination or hybrid of those 2 approaches. There's a system that was developed called a SmartCube, and they would put the laboratory rats inside of it, and there were lots of cameras around it that were hooked up to basically a supercomputer with artificial intelligence. They would administer to the rats things like known antipsychotics, antidepressants, and anxiolytics, and the computers would monitor every little nuance of the rat's behavior and be able to categorize, "Okay, well, this is what a rat looks like when given an antipsychotic, and this is what it looks like when given an antidepressant," and so on. And when they did that with this vast library of compounds they identified, one that looked like it had very strong antipsychotic potential and anxiolytic potential and some antidepressant potential, and what they pulled out of that was a TAAR1 agonist that also had serotonin 1A partial agonism. Completely unexpected.

The TAAR, which stands for trace amine-associated receptor, was only discovered really a couple decades ago. Trace amines themselves have been known for quite some time, almost a century, but the actual receptors weren't discovered until a couple decades ago, so this is a really new, fascinating field. And no one ever would have thought that a TAAR1 agonist could have been something that would have antipsychotic effects, but it began testing in early phase trials and proceeded on to later phase trials, and there was a positive phase II study which showed some really exciting potential benefits for people with schizophrenia.

Dr. Turck:
And your session also features data on muscarinic agonism as a potential therapy. So what can you tell us about that?

Dr. Chepke:
So this is another story I think is really cool: a couple decades ago, there was a company that was one of the largest companies in psychiatry, and they decided a number of years back to get out of making psychiatric medications. And there was one though that they had studied earlier on for Alzheimer's disease as a procognitive medication called xanomeline, and it was a muscarinic agonist that stimulated muscarinic receptors. They did notice kind of by serendipity that the people with Alzheimer's who had psychosis, it seemed to get better for most of them when xanomeline was given, and those on xanomeline didn't develop new psychosis compared to those on placebo at the same rate, so they tried it in a small schizophrenia trial. It seemed effective there. But again, side effects were a problem.

In the past several years, another company was able to license that medication and combined it with another medication that can help mitigate those cholinergic side effects, and there was a phase II study for that one that was also positive. And hot off the press, in the past several weeks, a phase III study showed positive results as well, so Psych Congress is going to be one of, if not the first, major conference to be able to discuss those really exciting breakthrough phase III results, so I can't wait to present those data to the audience.

Dr. Turck:
For those just joining us, you're listening to the *Psych Congress Action Center* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Craig Chepke about his Psych Congress sessions focusing on emerging treatments for schizophrenia.

Now to bring these two treatment options together, Dr. Chepke, how do they address current shortcomings and problematic adverse effects?

Dr. Chepke:
That's one of the really cool things about these two new treatments is that they operate off of a completely different mechanism than what we've had for 70 years. There is no binding to any D2 receptor, the dopamine 2 receptor, for either of them, and they both do seem to show in these early studies that they do have efficacy against positive symptoms but that they may have some really meaningful efficacy against negative symptoms of schizophrenia. Cognitive deficits, jury is still out there. And also, the tolerability profile is vastly different for both these agents from what we've seen in these early studies. There does not seem to be any propensity for the acute short-term movement disorders like akathisia, dystonia, or Parkinsonism for either of them. Also the weight gain and

metabolic profiles, there's no weight gain to speak of and the metabolic profiles have been unaltered compared to the patients on placebo in those trials, so it looks very different. And the adherence to antipsychotics, like adherence to medications in all chronic illnesses, honestly, is not great, as we all know, in people living with schizophrenia, and so if we have one or more agents that could have a very different and more favorable tolerability profile, that could also promote better adherence in our people living with schizophrenia. So we're seeing differences in both the efficacy and the tolerability profiles of these two products.

Dr. Turck:
And if we look ahead for just a moment, what are the next steps for these treatment options, and when might they become clinically available to patients?

Dr. Chepke:
So the muscarinic agonist is a little bit farther ahead. It does have the phase III data that was also positive, and the FDA has weighed in that that phase II study for it can be counted in terms of registration, so that company is planning to move ahead with submitting the data to the FDA sometime in the middle of next year. They're going to have some other new data from other short-term trials at the beginning of this coming year in 2023, and they're also working on long-term studies as well, so approval about 2 years from now maybe. And then the TAAR1 agonist, the phase III studies should be coming out with data in early 2023, in the January/February timeframe, so if we see positive results in those phase III studies, then they would probably be able to submit by the end of '23, early '24, approval late '24, or 2025 possibly. So we still have a couple years left to wait on these if, of course, all goes well with the forthcoming trials, but, gosh, just the excitement of thinking about what this could mean for people living with schizophrenia is just so exciting to me.

Dr. Turck:
And before we close, Dr. Chepke, were there any other thoughts you wanted to leave with our audience today?

Dr. Chepke:
Yes. I would say even putting these two new potential medications aside, we need to raise the bar for our expectations as clinicians for treating people living with schizophrenia. I hear all too often from colleagues that really it seems like their goal is just to keep the patients out of the hospital, and I don't think that's good enough. I think we need to raise our bar and really strive to get our patients with schizophrenia to remission, to be able to get them to have meaningful lives, to have relationships, to have the ability to get an education or to have a career, relationships, whatever it is their particular goals might be. Just keeping them out of the hospital is not enough because if we as clinicians don't expect that kind of outcome for our patients, that sets the tone for the patients themselves. How can they expect to do better if we don't expect they could do any better?

Dr. Turck:
These are exciting updates on some potential treatment options for our patients with schizophrenia. And I want to thank my guest, Dr. Craig Chepke, for sharing key insights from the 2022 Psych Congress. Dr. Chepke, it was a pleasure speaking with you today.

Dr. Chepke:
Thank you so much for having me. I had a blast.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit ReachMD.com/PsychCongressActionCenter where you can Be Part of the Knowledge. Thanks for listening.