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Time needed to complete: 51m

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## Exploring the Spectrum of Efficacy in Emerging Schizophrenia Therapies: From Positive to Negative to Cognitive Symptoms

### Announcer:

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### Dr. Correll:

Hello, welcome to Exploring the Spectrum of Efficacy in Emerging Schizophrenia Therapies: From Positive to Negative to Cognitive Symptoms. My name is Christoph Correll, and I'll be talking to you about the emerging treatments for the spectrum in schizophrenia covering those three domains I just mentioned. And then we summarize and conclude.

I will focus today on the emerging agents with novel mechanism of action in the development for the schizophrenia spectrum. We'll first talk about the TAAR1, trace amine-associated receptor 1 agonist, ulotaront, followed by two muscarinic receptor modulators, agonists, and positive allosteric modulators, xanomeline-trospium, as well as emraclidine. These three are under study or have been studied for positive and total symptoms. We'll talk about two agents briefly for negative symptoms. That is pimavanserin, which is a 5-HT2A inverse agonist, as well as roluperidone, which is a 5-HT2A antagonist/sigma 2 antagonist, that's for negative symptoms. And then finally, we'll wrap up with iclertin, a glycine transporter 1 inhibitor, that is under study for cognition in people with schizophrenia.

Alright, so what are trace amines? Trace amines are very interesting neurotransmitters. They're short forms of our current neurotransmitters that are mainly operating in the human brain. They are also in 100-fold lower concentration, and their respective receptors are also not what we're used to, like on the postsynaptic side, so that trace amines would be stored and the presynaptic vesicle, which is why they're sometimes called false neurotransmitters, since they're floating around inside of the presynaptic cells, or neurons, and they are chasing the trace amine-associated receptors.

Now, trace amines are something that we're all cognizant of, although we don't know it. They're actually part of what many of us like. They are part of seafood, cured meats, wine, cheese, and chocolate, all the stuff that feels good. So this is also because trace amines and the activation of the trace amine-associated receptors interact with serotonin, noradrenaline, and dopamine, and may be relevant for anxiety, depression, and psychosis. We also know from postmortem studies that people with schizophrenia seem to have an under-expression of trace amine-associated receptors, so that the agonism, the stimulation of such receptors may be relevant.

Two investigational drugs have been pursued. One is ralmitaront, and the taront stem in both of these words, tells you that the WHO has already acknowledged that this is a new class of medications. Ralmitaront is a partial agonist, so either a weak agonist or sometimes may work as an antagonist. And two studies were actually negative, one as monotherapy for positive symptoms and one as adjunctive treatment for negative symptoms. Ulotaront is a TAAR1 full agonist with a 5-HT1A full agonist, and had a positive phase 2 study. And I'll tell you about the results of the phase 3 studies right now.

As I mentioned, MDD, major depressive disorder as adjunctive treatment and generalized anxiety disorder are also targets for ulotaront. So the first study was actually positive with an effect size of 0.45, and worked for positive, negative, general symptoms, even

depression, and was very encouraging, with a difference from baseline of 17 points and placebo about 10 points. That gave rise to two big phase 3 studies that were, unfortunately, very disappointing. We only have a press release of them. The drug itself actually performed similarly, about 17 points or even 19 points in one dose arm. But the problem is, placebo outperformed itself over the phase 2 study. So instead of about 10 or 11 points, it had 14-point improvement in the one study and 19 points in the other, making all of the results negative. Now we don't know whether this means that it doesn't work overall, whether it will be used again in other studies, but the trace amine-associated receptor agonism actually is thought to reduce presynaptic dopamine tone by stimulating the autoreceptor on the dopamine receptor, on the dopamine terminal, and also internalize and reduce the affinity of the postsynaptic receptor. That makes it actually quite attractive for schizophrenia treatment, but we have to see whether this will be pursued further in psychotic disorders.

The second class of medications I want to talk about are muscarinic agonists or activators. Let's talk about acetylcholine that actually stimulates the muscarinic receptors, but also nicotinic receptors. So acetylcholine system has nicotinic and muscarinic receptors. The nicotinic receptors are ion-gated channel receptor-based fast acting. They also attenuate fast this is where smoking actually enhances cognition. We'll not talk about nicotinic receptors.

Let's talk about the muscarinic side of things. And these are G-protein-coupled receptors. They, once bound to, then set in motion a second messenger cascade. There are five of them, and 1, 2, 3, 4, 5, and they come in two families. The odd numbers, 1, 3, 5, actually are postsynaptic. And when acetylcholine binds to them, they're stimulatory. They give a goal signal. The even numbered receptors, M2 and 4, are presynaptic. That means they're auto receptors. And when presynaptic auto receptors are stimulated by acetylcholine, they then inhibit the downstream effect, that's important. Number one, M1, 3, 5, stimulatory; M2, 4, inhibitory.

And then there's also an orthosteric site at the muscarinic receptor, meaning this is the pocket where the endogenous neurotransmitter sits, in this case, acetylcholine. This is quite preserved across the five muscarinic receptors, so if you bind there, you might spill over into the effect of other muscarinic receptors. But then to the side, there's an allosteric binding site. It's a separate pocket, and that's very preserved and very specific for each of the five muscarinic receptors. And you can either be an orthosteric agonist or partial agonist, and you can also be an allosteric, positive allosteric modulator. You sit there and enhance the activity of endogenously-bound acetylcholine and also enhance the binding. Or there's also the possibility of negative allosteric modulators that somehow dampen the effect, but we'll talk about the increased effect.

Now, why is muscarinic receptor activation relevant for psychosis? It's relevant for two reasons. One is bottom up, the other one is top down. So what happens when the M4 receptor in the midbrain is actually stimulated by acetylcholine that comes basically from the hindbrain. Acetylcholine and dopamine are friends. They have a party together. When acetylcholine goes up, dopamine goes up. In psychosis, we want to reduce dopamine. So when you stimulate the M4 autoreceptor in the midbrain, you're reducing dopamine release in the striatum, because it goes from the midbrain in the ventral tegmental area into the striatum, and especially in the associated striatum where psychosis resides. So acetylcholine goes down, dopamine goes down in the ventral tegmental area and the striatum.

There is a second site of the M4 receptor, and that is at an interneuron, a cholinergic interneuron, in the associative striatum only there where psychosis resides. And when M4 receptors are stimulated there, they inhibit directly the release of dopamine in the striatum where we believe psychosis resides. So on two areas at that level, either midbrain or striatum, we reduce dopamine by reducing acetylcholine by a stimulation of the inhibitory M4 autoreceptor, that's bottom up.

Top down, M1, sits in the frontal lobe. When that's stimulated, acetylcholine goes up in the frontal lobe, that can improve cognition. But in terms of psychosis, the stimulation of M1 stimulates downstream effects, the break in the system, and that's GABA. GABA sits as an interneuron at the pyramidal excitatory glutamate neuron. And glutamate actually stimulates dopamine in the midbrain. So by stimulating M1, we're stimulating the break, GABA, and reduce the gas pedal, glutamate, to reduce dopamine.

So by hearing this, you now notice this is not just a receptor and a neurotransmitter action, this is a systems of neurotransmitters and interactions approach. And we hope that that can actually, more enduringly and maybe also more robustly, treat psychosis, because people might have different deficits in the midbrain, in a dysfunctional interneuron in the striatum, or too much EI imbalance, excitation/inhibition, not having enough GABAergic inhibition and too much excitation on the pyramidal tract.

Now, does that actually work? It does work. It worked in a phase 2B study with a muscarinic agonist, xanomeline, which spills over since it's orthosteric in the periphery and also has some pro-cholinergic peripheral side effects, nausea, vomiting, dyspepsia. Because of that, it was paired with a peripherally restricted anticholinergic called tropium, it's a combination pill, xanomeline and tropium, that then buffers these side effects and has some anticholinergic side effect profile itself, like constipation or dry mouth. But efficacy-wise, this was a very strong effect size in phase 2B first published as 0.75, recalculated 0.81; 0.2 was small, 0.5 is medium, 0.8 is large.

Now phase 2 studies, as we've seen with the trace amine-associated receptor agonist, ulotaront may not follow through in the clinical

phase 3 studies, but actually it did in two phase 3 studies. KarXT worked for positive, negative, and also total symptoms, as well as the moderate negative symptom score and CGI in the first phase 3 study with a 0.61 effect size, and then the second phase 3 study in a 0.60 effect size, with a number needed to treat for response at least a 30% reduction on the total PANSS score of 6 at week 3, and 4 at week 4 or 5. Xanomeline-trospium is given twice a day, with a titration over the first week being an agonist, and one wants to reduce the agonistic potential for side effects, which is also buffered by trospium, the peripheral anticholinergic.

In terms of pooled side effects from these three studies, there's about an 18.5% nausea rate, 17% constipation, 15% dyspepsia, 13% vomiting. But these side effects generally emerged in the first 1 to 3 weeks, and are then mostly reduced by the end of week 5.

Another approach is the positive allosteric modulation. So we have emraclidine, which, in a phase 1B study very early, with very small sample sizes, showed also at 6 weeks an effect size of 0.59 and 0.68 for total symptoms, being relevant for positive, negative, and general symptomatology. And looking at two CGI-Severity point jumps, there was still about 30% of patients who had that with a number needed to treat of 5, and having three jumps on the Clinical Global Impression-Severity, still 1 out of 7 patients had that, and the NNT was 7. So powerful modulation of the muscarinic system, which decreases dopamine tone.

In terms of side effects, xanomeline-trospium has the peripheral side effects and needed the buffer with the trospium, the anticholinergic, emraclidine being a positive allosteric modulator doesn't have that, so there are no pro- or anticholinergic side effects to speak of, which is obviously an advantage. Headache was a side effect, but similar also with the placebo arm.

For negative symptoms, there was a study with the roluperidone, which is a sigma 2 receptor antagonist and also 5-HT antagonist that worked in phase 2, and then in phase 3 it didn't. We had pimavanserin that worked in phase 2, and in phase 3 it also didn't work. So we, at the moment, do not have a good answer for negative symptoms with the studies and the agents under development.

And then finally, there are cognitive symptoms that we also need to improve. Here, KarXT, xanomeline-trospium, actually in all three studies, phase 2 and phase 3, had an effect on cognition in the 50% of patients who had at least one standard deviation of cognitive dysfunction below the general population. And there, the effect size was about 0.5 which is respectable, although this was in a context of an active study in acute patients. So people could have also improved, because their positive and negative symptoms improved, although the correlation between positive, negative, and cognitive symptoms was not large.

And then the final point is that we have a glycine transporter inhibitor that enhances NMDA glutamatergic function in areas where cognition is relevant. And here, the iclepertin had good effects in phase 2, better for people who are only on one antipsychotic, with more negative and cognitive symptoms, not on benzodiazepines than in younger patients and those with a shorter illness duration. At that study, there was no effect significant for functioning. And that's often required by the regulator, so we will have to see whether in phase 3 these results will pull through, and whether there's also not just a cognitive but also functional results.

So encouraging results after 7 decades of only postsynaptic dopamine blockade for muscarinic agonism or positive allosteric modulation, mixed results for TAAR1 agonism, negative and mixed results for roluperidone, as well as for pimavanserin, and that's for negative symptoms. And adjunctive iclepertin is still under study for cognitive dysfunction. So hopefully the data that were found in these clinical trials will translate into enhanced efficacy in clinical care for positive and maybe also other symptom domains.

Thank you for your attention.

**Announcer:**

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