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D2 Antagonists Limitations and Challenges: A New Era in Schizophrenia Pathophysiology

Announcer:
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Dr. Citrome:
Hello, I'm Dr. Leslie Citrome, Clinical Professor of Psychiatry and Behavioral Sciences at New York Medical College in Valhalla, New York. We're going to talk about dopamine pathways, and specifically dopamine D2 antagonists that we use to treat schizophrenia. However, there has been a new understanding on where these pathways are in the human brain. Let me take you through that.

We've known for years that there are several dopamine pathways in the human brain. We've heard about the mesolimbic pathway and the mesocortical pathway and the nigrostriatal pathway, as well as the tuberoinfundibular hypothalamic pathway for years. We've understood for a long time that deficiencies in dopamine signaling in the mesocortical pathway can explain negative symptoms and cognitive impairment. We've also understood that the nigrostriatal pathway controls our movements. And then there's the mesolimbic pathway, originating from the ventral tegmental area in the midbrain, innervating the ventral striatum, where excess dopamine explains the production of hallucinations and delusions. So what do we do? We use dopamine D2 receptor blockers to block the excessive dopamine signaling in the mesolimbic pathway, hence treating hallucinations and delusions.

Unfortunately, this understanding of the human brain was incorrect. Now we have a better view of the brain using modern imaging techniques and have identified a refinement of this model. I mention this to you because you'll see a lot more of this in the literature, and it's confusing. You're going to hear about a nigrostriatal pathway that actually explains hallucinations and delusions, whereas in the past, the nigrostriatal pathway was almost exclusively considered to be controlling our movements.

So what's new here? Well, there is a part of the substantia nigra in the human brain that innervates another part of the striatum called the associative striatum. It is this pathway that is overactive in people with schizophrenia and that blocking dopamine D2 receptors there in the associative striatum will treat hallucinations and delusions. It may sound like a subtle difference, but when we say nigrostriatal pathway, it does not necessarily translate to only movements that we're worried about.

So let's move forward now and think about blockade of dopamine D2 receptors in the nigrostriatal pathway, pathway number 1, that explains hallucinations and delusions. It's good to block dopamine D2 receptors there; however, it will also block dopamine D2 receptors in the other pathway that controls movements, nigrostriatal pathway number 2, originating in the human brain in another part of the substantia nigra, and going to the dorsal striatum or sensorimotor striatum. And blockading the D2 receptors there will result in drug-induced Parkinsonism. So that's our double-edged sword in terms of treating psychosis, right? We can treat psychosis, but with the older agents, in particular, we'll also induce movement disorders.

There's also the tuberoinfundibular hypothalamic pathway, where dopamine D2 blockade there will result in elevation in prolactin and perhaps amenorrhea, galactorrhea, and sexual dysfunction. So that's one aspect of the limitations of blockading or antagonizing dopamine D2 receptors.

There are others, of course. Patients don't necessarily respond adequately to dopamine D2 receptor blockade; they may have residual symptoms and inadequate treatment response. That happens in about 1 out of 3 patients who don't respond. Negative and cognitive symptoms will perhaps persist as well. And then we have those variety of side effects. I mentioned drug-induced Parkinsonism, thanks to dopamine D2 blockade in the dorsal striatum. Ultimately, we may even have tardive dyskinesia. We also talked about prolactin elevation.

There are other receptors involved with antipsychotic treatment, and they can result in side effects such as sedation and weight gain and, in general, metabolic dysregulation. The bottom line is that all currently available antipsychotics work essentially via similar mechanism, a dopamine D2 receptor blockade as well as other receptor antagonism and partial agonism and whatnot, that differs from drug to drug. The bottom line, though, is that we have plenty of adverse events to consider.

Which ones do patients find troublesome? Well, we can ask them. Here are the frequency of antipsychotic side effects in patients with schizophrenia, as determined by a survey of about 900 community-dwelling adults with schizophrenia. The orange bars represent dopamine D2 antagonism-related adverse events, so restlessness and feeling jittery could be akathisia, for example. Decreased interest in sex can also be a consequence of D2 blockade, perhaps resulting in elevation of prolactin. Tremors or other motor disorders can also be observed. So these are problems that we would like to avoid.

There's also these blue bars here. And the blue bars represent adverse events that may be related to the other receptors that antipsychotics may bind to, whether it be serotonin receptor subtypes or adrenergic receptors. We can encounter problems with concentration, insomnia, weight gain, sedation, dizziness, constipation. So there's room for improvement, obviously, in terms of tolerability, if only we can go beyond dopamine D2 blockade in terms of potential treatments.

There's also the notion that some of our patients with schizophrenia do not respond to dopamine D2 receptor modulation. And we know that this is encountered in a large subgroup of patients, roughly 1/3. Well, it turns out, if we take a look at neuroimaging studies, poor response to antipsychotics is associated with actually an abnormality in glutamate levels. In a particular area of the brain, we can identify a dysfunction that may be a good target for novel treatments.

Described here on this slide is a cross section of the brain that describes the anterior cingulate cortex, or ACC. The ACC is effective. It's involved in emotion assessment, emotion-related learning, autonomic regulation, projects widespread to other areas of the brain that are important for emotion and memory and reward. And many of our patients with schizophrenia have a dysfunctional ACC, may be related to How the glutamate circuitry is dysregulated.

Let's talk about now another theory of schizophrenia that goes beyond dopamine. Ultimately, it will lead to a more appropriate regulation of dopamine, but it's upstream of dopamine. The glutamate hypofunction hypothesis of schizophrenia has been around for a while, and the suggestion is that psychosis and schizophrenia may be the result of a hypofunctional NMDA receptor on GABA interneurons in the cortex. Now, NMDA receptors are glutamate receptors. GABA interneurons are inhibitory interneurons. If you have a hypofunctional NMDA receptor on the GABA interneuron, you have a dysregulation of the network. The hypofunction may lead to over activation, actually, of downstream glutamate signaling. This is because through the network, we have a release of any inhibition, ultimately leading to too much glutamate. Overactive glutamate signaling leads to overactive dopamine signaling to the associative striatum that we just talked about earlier, leading to hallucinations and delusions.

So ultimately, glutamate controls dopamine output, if only we can regulate glutamate better. So that's one avenue of interest in terms of the development of new medications to treat schizophrenia.

Another one is muscarinic cholinergic regulation. And the muscarinic cholinergic hypothesis of schizophrenia is also upstream of dopamine. In the 1950s pro-cholinergic drugs were observed to increase lucid intervals in patients with psychosis, but were not well tolerated, and further development was abandoned until now. It turns out that cholinergic systems directly modulate striatal dopamine function in areas associated with the positive symptoms of schizophrenia, and they also regulate descending glutamate pathways that interact with striatal dopamine circuits. So maybe this is the answer.

It turns out that muscarinic receptor and M1/M4 mouse knockout models replicate the phenotype of schizophrenia and muscarinic agonists, especially for M4 receptors, improve positive and negative symptoms of schizophrenia in mice models and in people.

Postmortem studies show reductions in M1 and M4 receptor expression in brain regions implicated in schizophrenia. About 1/4 of our patients with schizophrenia have over a 75% reduction in M1 receptor expression.

On this slide, you'll see cross sections of the human brain where M1 and M4 receptor expression is predominant. Just in the areas of the brain, we need to better regulate. The search for a non-D2 mechanism continues, and there's been substantial improvement in our methodology in doing so. And of about 500 clinical trials from 20 - well the past 20 years, total patient enrollments for non-D2

compounds was actually greater than that for research with traditional compounds. We have no launches yet of a new drug that can treat psychosis without directly blocking dopamine D2 receptors, but we're pretty close.

Let's take a look at some of them. Here are investigational non-D2 compounds for schizophrenia: emraclidine, KarXT, and ulotaront. Emraclidine is a highly selective positive allosteric modulator of M4 muscarinic receptors. It's currently in phase 2 of clinical development. KarXT is short for xanomeline-trospium combination. It's an M1/M4-preferring muscarinic agonist combined with a anti-muscarinic agent for tolerability purposes, and that's in phase 3 actually; it's in front of the FDA for a decision coming up soon later this year. Ulotaront on is a trace amine receptor agonist with serotonin 5-HT1A agonist activity. It is in phase 3 of clinical trial development, but it's had some hiccups along the way, and further development is being considered, but not yet decided upon as far as I understand it.

So the bottom line is that dopamine D2 receptor blockade has been the mechanism of action of all our antipsychotics available to date, with some variations amongst the second-generation antipsychotics that translates to a variety of different adverse event profiles. They all work, but they're all potentially associated with adverse events we'd rather avoid, rhetorically. We can perhaps avoid that by not blocking dopamine D2 receptors directly, and yet treating positive symptoms. We can do that upstream with glutamatergic agents of one kind or another, or muscarinic agents of one kind or another. That downstream will help regulate dopamine, so that there is a decrease in excessive dopamine signaling, and hopefully a decrease in hallucinations and delusions, in drugs that have a different tolerability profile and maybe a different efficacy profile for those who didn't respond to the traditional agents.

That's my hope, and let's keep our fingers crossed. Until the next time.

Announcer:
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