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Residual Symptoms: Dealing with the Limitations of Existing Treatments

Announcer:
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Dr. Meyer:
Hi, everybody, this is Dr. Jonathan Meyer, Voluntary Clinical Professor of Psychiatry at the University of California, San Diego, here to talk Residual Symptoms: Dealing with the Limitations of Existing Treatments.

And really what it comes down to, is that all of our existing antipsychotics predominantly work via D2 blockade, and that's been real helpful in some areas. But there are some areas where it hasn't been so effective, we really don't have a number of options within our existing antipsychotics for negative symptoms, with one exception, which I'll mention in a second. We're pretty good about treating positive symptoms. But cognitive deficits are another area where D2 blockade really isn't too effective. Sometimes we can moderate aggression, but there are forms of aggression that don't respond to D2 blockade, when people are depressed or antipsychotics are often not so good about that.

Where we mostly have been helpful is in reducing dopamine neurotransmission, and what we call now the associative striatum, or in animal models, the mesolimbic pathway. That's been great. It's been very helpful. But clearly, we have a lot of limitations on what we can get from D2 blockade. And one evidence for that is the fact that probably a quarter of individuals don't respond to traditional antipsychotics, meaning anything other than clozapine. And we have understood now by imaging these individuals that their problem may not be a primary dopaminergic problem, but actually a glutamate problem. Clozapine is the only thing right now that works for treatment-resistant schizophrenia, and whatever its magic is, is not mediated via D2 blockade; it's a very weak D2 antagonist. It has a number of other properties.

But you see in the fourth bullet here, that we look at imaging studies of patients with treatment-resistant schizophrenia, that it's not a dopaminergic problem presynaptic way with positive symptoms, but maybe a glutamate problem. And guess what, when you put them on clozapine, some of these issues normalize. So really, this helps us understand the neurobiology of schizophrenia broadly, and specifically why some people, even for positive symptoms don't respond to D2 modulation.

And certainly, for negative symptoms, it’s a more complicated story. As you can see from this circuit diagram, negative symptoms are very complex, involve a number of systems, including prefrontal cortical, as well as subcortical, especially the reward pathway, we think fundamental to some of this might be insufficient D1 mediated neurotransmission. The point being is that D2 blockade is simply not an effective treatment for patients who have persistent primary and negative symptoms.

To understand negative symptoms, this is the way we conceptualize it now. There are five dimensions, if you're not familiar with them, blunted effect, alogia, anhedonia, asociality and avolition. But these really cluster into two groups. We have what's called the diminished expression group, which is blunted effect and alogia. And we have avolition, asociality, anhedonia, which is part of the evolution apathy group. D2 blockade, not so good at making these better. And as you can see, these are quite common. And this has been an important

issue in the treatment of schizophrenia patients, that we can control their positive symptoms, but some are actually very disabled by the presence of persistent primary negative symptoms.

People throw in a lot of meds at negative symptoms. Here's a summary of a lot of the studies which have been done. What's interesting is you see that antidepressants sometimes work. And we think maybe in some of those patients, what we're actually treating are subsyndromal mood symptoms, which respond to an SNRI or an SSRI. And certainly, if you have a patient with schizophrenia, without a history of mania, with negative symptoms, it's worth a trial of a traditional antidepressant. But many of the other strategies we have tried really don't work very well.

But there is one option, and this is relatively newer data of the partial agonist cariprazine, which was studied in a long-term trial of stable schizophrenia patients with persistent negative symptoms, versus a known antipsychotic, risperidone. The big difference mechanistically is of course, that cariprazine is a partial agonist at both D2 and D3 receptors, whereas risperidone as a traditional serotonin dopamine antagonist. We can see over time using the metric of improvement of 20% or more in negative symptoms, that cariprazine does separate from risperidone. We would like to see a replication of this, but it shows you that perhaps there is something we can do with negative symptoms that is not remediated with a traditional D2 antagonist.

Lastly, one of the more disabling features of the illness, one which starts even before the onset of positive symptoms, is cognitive dysfunction. There's a number of neurotransmitter systems and circuits involved, none of which are actually remediated with D2 blockade. An important finding in recent years is that many schizophrenia patients have diminished muscarinic M1 receptor expression, some quite profoundly, but this remains an important aspect of the illness which is simply not addressed via existing treatments.

In summary, we have been very thankful for D2 blockade. Iit's helped a number of people with their positive symptoms, but we recognize there are significant limitations, especially for some of the more persistent and disabling features of the illness, such as negative symptoms and cognitive dysfunction, and sadly, for that fraction of individuals who have treatment resistant schizophrenia and don't respond to D2 blockade.

This is Dr. Jonathan Meyer. Thank you for watching this episode.

Announcer:
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