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Addressing the Hidden Burden of Negative Symptoms in Schizophrenia

Announcer:
You're listening to *NeuroFrontiers* on ReachMD, and this episode is sponsored by Bristol Myers Squibb. Here's your host, Dr. Alexandria May.

Dr. May:
This is *NeuroFrontiers* on ReachMD, and I'm Dr. Alexandria May. Joining me to discuss negative symptoms in schizophrenia and how we can manage them is Dr. Michael Halassa. He's the Director of Translational Research and a Professor in the Department of Neuroscience, as well as a Professor in the Department of Psychiatry at Tufts University School of Medicine in Boston. Dr. Halassa, welcome to the program.

Dr. Halassa:
Thank you.

Dr. May:
To start us off, Dr. Halassa, what do we mean when we talk about negative symptoms in schizophrenia? And how are they distinct from the more widely-recognized positive symptoms?

Dr. Halassa:
Yeah, it's a great question. I think it's hard to describe in words what negative symptoms are because you have to see them. The main textbook description that distinguishes positive and negative symptoms is that positive symptoms are things that are added to behavior. For example, hearing voices or having unusual thought content—what we refer to as hallucinations and delusions—are positive symptoms because they do not exist normatively in healthy adults. Negative symptoms are the absence of behavior, and they generally cluster into two main groups: expressive and motivational. So for example, you have the absence of emotional reactivity. People appear to be flat. People do not socially engage in the manner that's expected. It's cross cultural; it's observed across all types of environments, cultures, etc. And then when it comes to the motivation to act in the world, people appear to be withdrawn and uninterested in work or in any kind of effortful activity. So that's generally how negative symptoms are understood.

But in practice, the most obvious way a provider can tell what a high negative symptom burden in an individual is, is by sitting down with a patient and not saying anything, and seeing at what point the patient would spontaneously engage in a conversation. Like with you and I having a conversation here, if I just sat there, it would be pretty odd. But that spontaneous human engagement when you're in a social setting or the absence of that is a telltale sign of negative symptoms.

Dr. May:
And building on that, can you shed some light on the neural pathways or brain circuits that are thought to be involved in driving negative symptoms?

Dr. Halassa:
There are multiple different hypotheses. I think the strongest would be the hypotheses around frontal function. So the frontal lobe generally is the machinery that we all have to set goals and action plans, and it's a flexible part of the brain that builds models of the world and allows us to act on those models. The frontal cortex requires subcortical machinery, areas like the basal ganglia, thalamus, etc. There are these large-scale networks and loops in the brain that are involved in building these internal models of the world, maintaining them, and flexibly switching them.

There are many different components of this process that could be altered in a way that your model of the world is very simple. For example, you can't build complex models and reason through different decision trees, and that's simply the absence of whatever drive the frontal cortex gets. So that's one hypothesis.

Dr. May:
You mentioned a lot about the brain regions, but a little bit about the neurotransmitters or deficiencies in neurotransmitters that may be at play. Could you expand a little bit more on that?

Dr. Halassa:
Sure. 90 percent of neurons in the brain use glutamate to communicate with one another. That's fast synaptic transmission. When you want to get something from your frontal cortex to your visual cortex or to whatever, that fast communication across the brain is mediated by glutamate. Most of the brain and most of the cortex and subcortical areas use that for fast communication. The rest is mostly interneurons that use GABA, and those are fast inhibition. So a lot of the things have to function in a balanced way where you have fast excitatory messages balanced by inhibition.

On top of that, there are these various neuromodulators that modulate the circuit function at slower timescales, and those include dopamine, norepinephrine, and acetylcholine, for example. And the two transmitters that are relevant to schizophrenia and psychosis are dopamine and acetylcholine because they're the targets for the two major classes of antipsychotics: the traditional, dopamine-targeting antipsychotics—risperidone, olanzapine, clozapine, etc.—and the newer class of agents: the muscarinics that target acetylcholine. Xanomeline is the first-in-class muscarinic agonist that targets a specific subset of acetylcholine receptors in the brain. And part of them are enriched in the frontal cortex, and maybe that's part of the reason why this particular class of medication has good effects on negative symptoms.

Dr. May:
What have you noticed from patients and caregivers about how negative symptoms affect things like relationships, work, or motivation? And why do you think these symptoms often fly under the radar?

Dr. Halassa:
A lot of the times, they're hard to recognize because they're subtle. If somebody's not interacting, you can have all kinds of high-level cognitive theories about why somebody is not wanting to interact with you. It could be about you, or it could be about who knows, right? Given that we don't know exactly what's going on, that would lead to somebody expressing negative symptoms; in some individuals, it seems that the individual still craves social interactions, yet they are unable to express that craving in a way that other people can understand.

I have a colleague who has a theory about why this works, and the theory is that it's a memory capacity, which people have recognized in schizophrenia, but it's particularly in the social domain. In order to interact with people, you need to be able to remember facial expressions; you need to be able to express to match each person you interact with. If you don't have that memory, then you default to a single facial expression for all social interactions, and that's what negative symptoms may look like. It's simply the brain's default when it can't remember how to match different social interactions to individual settings.

Dr. May:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Alexandria May, and I'm speaking with Dr. Michael Halassa about the hidden burden of negative symptoms in patients with schizophrenia.

So given the impact of negative symptoms, Dr. Halassa, are there any practical strategies or frameworks that can help us identify these symptoms in patients?

Dr. Halassa:
It's important to give the patient the opportunity to spontaneously engage and evaluate their level of spontaneous engagement. I can tell you what it looks like. You can go into somebody's room on the inpatient unit—and I've done this with a nurse practitioner that I was training—and she wanted to lunge into interviewing the patient. I said, "Don't do anything. Why don't we just sit by the bed?" And we did, and the patient didn't say anything. And she was like, "This is pretty weird." I said, "Yeah, but you would not know until you do this." Just sit there. And we were almost like furniture to the patient. The absence of that spontaneous engagement should be kind of a sign to keep in mind and file.

Dr. May:
Now, if we turn to treatment strategies, what are some of the current and emerging approaches being explored to better address schizophrenia symptoms, especially those that persist?

Dr. Halassa:
A lot of times when people end up in treatment for schizophrenia, the most pertinent symptoms are the positive symptoms. People are hearing voices, are saying things that are concerning their family members, are having unusual thought content or suspiciousness, etc. I mostly practice in the inpatient setting, and I see people with what we would consider a high burden of positive symptoms. So people are really impaired and are unsafe to be in any setting other than an inpatient facility. So under those conditions, the general approach is once you establish that this is a primary psychiatric or psychotic illness, use high-efficacy antipsychotic medications; the two most commonly used ones are risperidone and olanzapine.

So risperidone is a pretty strong D2, or dopaminergic-blocking, agent. Olanzapine is weaker, but it has a high efficacy because it targets a number of other adjacent receptors to dopamine. Those medications are not particularly efficacious when it comes to high negative symptom burden. Sometimes, a very high positive symptom load can have secondary negative symptoms associated with it. And when you treat the positive symptoms, people just get better overall and are able to engage, and so that, I would say, would be more like secondary negative symptoms. But sometimes, there are primary negative symptoms that, even when you treat the positive symptoms, they persist. And what's even more complicated is that dopamine-targeting antipsychotics can make those symptoms even worse. Clozapine is an exception. And interestingly, clozapine is not a particularly strong D2 blocker, although it is highly efficacious.

Given all of that, the development of medications that target negative symptoms more efficaciously would be great. And it turns out that this rise of muscarinics with XT—xanomeline being the first in that class—is a good sign because from what I've seen, it looks like it's efficacious when it comes to negative symptoms in particular. When we gave this patient XT, and we came back 48 hours later, he jumped out of bed. He's like, “What's up? How are you guys doing?” That was mind-blowing.

I get emails and calls from providers and family members across the country asking questions and also reporting similar observations with the start of this medication. It's not everybody, but there is a sizable portion of people that when they are given the muscarinics in general, they experience what people have described as almost an awakening phenotype where, prior to that, they were withdrawn. They were not spontaneously engaging. They get this medication, and all of a sudden, people just start to spontaneously engage. To the degree that we've been able to see this medication in action over the last 14 months, I think it's looking pretty promising in that particular domain.

Dr. May:
And if we take a broader look before we close, Dr. Halassa, how should we be reshaping our definition of success in managing schizophrenia, particularly when we factor in the burden of negative symptoms?

Dr. Halassa:
So I think society has accepted that what our jobs are for these individuals is to just keep them safe. The dementia praecox is there to stay, and there's not much we can do about that because it is what it is. And I just don't think that's true anymore. We have levers now. We can basically make the positive symptoms better, which increases function to some degree. There are people who, once you stabilize their positive symptoms, are fine. They can actually function. They get jobs, etc. They're very high functioning. But that's not who most people are. Most people live with the burden of negative and cognitive symptoms.

And I think now with the muscarinics, we at least have the initial idea that those things are targetable. I don't think we have the medication that does it for everybody. I think it's moving the needle, for sure. But I think we have a lot of work left to do.

Dr. May:
As those final comments bring us to the end of today's program, I want to thank my guest, Dr. Michael Halassa, for joining me to discuss the impact of negative symptoms on schizophrenia patients and how we can better manage them. Dr. Halassa, it was great having you on the program.

Dr. Halassa:
Thank you. It was great to be here.

Announcer:
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