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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Negative Symptoms in Schizophrenia: Identifying and Managing the Hidden Burden

Announcer:
You're listening to *On the Frontlines of Schizophrenia* on ReachMD. And now, here's your host, Dr. Brian McDonough.

Dr. McDonough:
I'm Dr. Brian McDonough. Joining me to discuss the impact of negative symptoms on patients with schizophrenia as well as strategies to better manage them is Dr. Ahmed Makhlouf. He is the Medical Director of the Brigham and Women's Hospital Psychosis Program and Instructor in Psychiatry at Harvard Medical School. He is also an investigator at the Center for Brain Circuit Therapeutics at Mass General Brigham. Dr. Makhlouf, welcome to the program.

Dr. Makhlouf:
Thank you so much for having me, Dr. McDonough.

Dr. McDonough:
So why don't we start with some background, Dr. Makhlouf. Can you tell us what negative symptoms in schizophrenia are and how they differ from the positive symptoms that often get more attention?

Dr. Makhlouf:
Absolutely. In general, when people think of schizophrenia, they think of positive symptoms. They think of hallucinations, delusions, thought disorganization, or disorganized behavior. But there's also a group of symptoms that we call 'negative symptoms' that are a crucial component of the syndrome of schizophrenia. We divide them into primary and secondary negative symptoms. Primary negative symptoms are part of the disorder itself, and secondary negative symptoms are usually secondary to medications or comorbid conditions.

But negative symptoms in general—and I'm talking specifically about primary negative symptoms—fall into two major groups: expressive deficits, like apathy, blunted affect, and alogia—poverty of speech—and motivational deficits, like avolition—poor or limited motivation—and anhedonia—difficulty enjoying things or getting pleasure out of previously pleasurable activities.

Dr. McDonough:
And if we look at these symptoms from a neurobiological standpoint, what do we know about the mechanisms driving them?

Dr. Makhlouf:
It's usually helpful to look at negative symptoms from a brain circuit perspective. So for example, if we look at dopaminergic pathways, we're looking at the mesocortical dopaminergic pathway starting at the ventral tegmental area, which connects the midbrain to the prefrontal cortex. When there is lower dopaminergic tone in that pathway, that leads to expressive deficits.

The other relevant dopaminergic pathway is the mesolimbic pathway. It also starts at the VTA and connects the VTA to the ventral striatum and the nucleus accumbens. When there's lower dopamine signaling in that pathway, that leads to reduced reward anticipation and motivation, leading to avolition and anhedonia.

There are also serotonergic pathways that we know are involved because the antipsychotics, especially second-generation

antipsychotics, are—in a lot of cases—serotonin receptor blockers. There are glutamatergic pathways that are probably involved, and we know that because of ketamine and how it might contribute to psychotic symptoms in patients who receive it as a substance or as a treatment for other conditions.

Dr. McDonough:
Now, what about the patient perspective? How do these symptoms show up in day-to-day life, and is there anything that caregivers often notice that we as clinicians might miss?

Dr. Makhlouf:
Negative symptoms, in general, don't tend to be very distressing to patients. That has to do with limited insight into the disorder of schizophrenia. But we've heard patients say things like, 'People say I look blank or cold, but I don't mean to,' or 'I just go through the motions every day.' But usually caregivers or medical teams observe negative symptoms and are able to report negative symptoms more than patients, and they report apathy, poor hygiene, and social withdrawal. A common comment that we get from caregivers is that the patient is not themselves anymore. And sometimes, especially if treatment is successful, they say things like, 'We can see glimpses of that patient's personality coming back.'

Dr. McDonough:
That has to be very rewarding. And for those just tuning in, I'm Dr. Brian McDonough, and I'm speaking with Dr. Ahmed Makhlouf about managing negative symptoms in patients with schizophrenia.

So, Dr. Makhlouf, now that we have a better understanding of these negative symptoms, let's switch gears and focus on how we can better monitor and manage them. Given that patients may not always report these symptoms, what tools or assessments can help us identify them more reliably?

Dr. Makhlouf:
I would say the first thing is getting collateral from family and caregivers because, in general, we're able to report these symptoms more accurately. Second, we rely on symptom scales. So for example, the Brief Negative Symptom Scale has subscales for each of the five A's in addition to distress that patients report. There is a Clinical Assessment Interview for Negative Symptoms, and it differentiates expressive deficits, like flat affect and alogia, from motivational deficits, like avolition and anhedonia. There is the Scale for Assessment of Negative Symptoms, which is a very comprehensive scale for negative symptoms; it's a 25-item scale. There's also the Negative Symptom Assessment, which is a little bit less comprehensive than the SANS, but we use that in clinic. It also has an even briefer form that might be more suitable for very busy clinical settings, which is the NSA-4—the Negative Symptom Assessment- 4.

These structured tools or symptom scales are important because primary negative symptoms can be mistaken for depression or motivational side effects—this comes back to primary versus secondary negative symptoms.

Dr. McDonough:
Now, once those symptoms are identified, what treatment strategies are most effective for addressing them?

Dr. Makhlouf:
There are a few strategies. The low-hanging fruit is medications—psychopharmacology. There was a pivotal head-to-head trial comparing partial agonist cariprazine to risperidone, and it showed that cariprazine led to greater improvement in negative symptoms in patients who had predominant negative symptoms. So the D3-preferring properties of a partial agonist like cariprazine might help enhance reward and motivation circuitry.

There's also a newer medication, xanomeline-trospium. We've seen some improvement in negative symptoms in very treatment-resistant sick patients on clozapine. By adding this new medication to clozapine, we're starting to see some improvement in negative symptoms. A patient that we treated earlier this week with xanomeline-trospium, in addition to clozapine, described the new medication as a weak stimulant.

There are also some psychosocial approaches: CBT for psychosis or for negative symptoms. Behavior activation, family therapy, and social skills training can also be very helpful. Approaching negative symptoms and schizophrenia in general, from a rehab perspective can be very effective—so vocational rehab, community support, occupational therapy, and day programs.

There are also neuromodulation therapies or brain stimulation therapies like ECT. Regarding ECT for negative symptoms, specifically, the studies have small sample sizes and the effect sizes are small, but what we know is that ECT plus an antipsychotic is at least better at controlling negative symptoms than monotherapy with antipsychotics.

Dr. McDonough:
And if we take a step back and look at the big picture before we close, Dr. Makhlouf, how should we redefine what success looks like in schizophrenia treatment when negative symptoms are present?

Dr. Makhlouf:
I think focusing on making sure that patients thrive and they're not just surviving with symptom reduction is crucial. Make sure we're focusing on seeing the patient as a person and focusing on social engagement, motivation, and functional reintegration into society, and make sure patients have a purpose, goals, and things to look forward to in life. The involvement of caregivers and the community is extremely important. Some people think of schizophrenia as a neurodegenerative condition, and approaching it from a rehab perspective and seeing it that way might be helpful in making sure these patients succeed.

Dr. McDonough:
As those final comments bring us to the end of today's program, I want to thank my guest, Dr. Ahmed Makhlouf, for joining me to discuss the hidden burden of negative symptoms on schizophrenia patients and how we can help address it. Dr. Makhlouf, it was great having you on the program.

Dr. Makhlouf:
It's been an absolute pleasure, Dr. McDonough. Thank you for having me.

Announcer:
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