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Caring for Treatment-Resistant Schizophrenia: Is DBS the Answer?

Dr. Wilner:
Although there's currently no cure for schizophrenia, it can be managed with therapy and medication – for some patients, that is. In fact, up to one half of patients with severe symptoms don't respond to medication. So, how are we to care for this large percentage of patients living with treatment-resistant schizophrenia?

Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner and joining me to talk about his recent case study on using deep brain stimulation for treatment-resistant schizophrenia is Dr. Nicola Cascella. Dr. Cascella is an Assistant Professor of Psychiatry and Behavioral Sciences at Johns Hopkins University School of Medicine. Dr. Cascella, welcome to the program.

Dr. Cascella:
Thank you for having me.

Dr. Wilner:
To start us off, Dr. Cascella, can you tell us which symptoms are associated with treatment-resistant schizophrenia?

Dr. Cascella:
Three main domains of symptoms are associated with schizophrenia in general and then, of course, some of the symptoms are resistant to treatment. The domain of positive symptoms, which include the presence of hallucinations and delusions, as well as thought disorders and disorganized behavior. The domain of negatives, which include this lack of a sense of purpose on the part of the patient, and what all psychiatrists describe it as is distraction of personality, in which there is a lack of endeavor for the usual activities that the patients had prior to the onset of the illness. And then there is a series of domain of cognitive symptoms which include lack of attention, psychomotor speed, which is almost the hallmark of neuropsychological dysfunction in patients with schizophrenia.

Dr. Wilner:
So, why doesn't regular therapy and anti-psychotic medication work for so many patients?

Dr. Cascella:
The accepted theory about the working of anti-psychotic medications is that they block dopamine receptors and it's possible that there is an increased dopaminergic tone in patients who respond to the treatment – actually, it has been shown with brain imaging using positron emission tomography, or PET, that patients who tend to respond to anti-psychotic medications have an increased production of dopamine. Otherwise, for patients who do not respond to treatment, they do not have an increased production of presynaptic dopamine, so it's possible that the entire physiopathology of no response to treatment is different in these two populations of patients with schizophrenia.

Dr. Wilner:
So, there's a spectrum of pathophysiology, you think, within the diagnosis of schizophrenia?

Dr. Cascella:
Yes. There is a spectrum of physiopathology and, in fact, it's possible that within this spectrum, a group of patients will become – or even from the onset of the illness – are resistant to treatment then go on to respond to a medication like clozapine, for example that is currently used as the next best step when other anti-psychotic medications fail. The treatment-resistant population is comprised by a subgroup of patients, maybe around 30 percent, 25 percent of patients who fail to respond to clozapine and those are the ones that at least initially caught our attention and our thinking about using deep brain stimulation.

Dr. Wilner:
So, you've identified a group of patients that don't respond to usual therapy. How did you get to deep brain stimulation from there?

Dr. Cascella:
We looked at deep brain stimulation because, in the field of neurology, this particular treatment has been used for patients with Parkinson's disease or other movement disorders that fail to respond to medications, for example. And before we did our first case, there has been over the last ten years interest in the use of DBS in the field of psychiatry, in particular for treatment of those patients with major depression who are treatment-resistant. And patients with OCD, or obsessive compulsive disorder, who are also treatment-resistant. The use of the DBS in this population has been encouraging; not all patients, of course, responded to the stimulation but a good percentage of them found the relief from very debilitating symptoms. With this in mind, we took a look at the use of deep brain stimulation in schizophrenia.

Dr. Wilner:
So how did you test whether it would work or not?

Dr. Cascella:
Of course we had to choose an area of the brain where to place the electrodes for the stimulation of this brain area. And looking at the anatomy and the physiology of the brain it is well-known that there are parallel circuits that start in the cortex and are followed down to the basal ganglia and then there are two major output nucleus or nuclei that form the basal ganglia, which is a substantia nigra pars reticulata, and the GPi, or internal part of the globus pallidus that return that information which is worked up in the basal ganglia to the medial dorsal nucleus of the thalamus. And from there to the entire cortex. So, the idea we had is: how can we modulate the medial dorsal nucleus of the thalamus? And one way to do that was to place the electrodes in the substantia nigra pars reticulata. The hope was that we could avoid a motor circuit of the nigra and affect the limbic circuit, which we thought was related to the positive symptoms of schizophrenia, as well as the cognitive circuit that would eventually improve cognition in our patients.

Dr. Wilner:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner and I'm speaking with Dr. Nicola Cascella about his recent study exploring whether deep brain stimulation could be effective for treatment-resistant schizophrenia.

So, let's get back to your study, Dr. Cascella, what did you find? What were the results?

Dr. Cascella:
The results were extremely rewarding in the sense that it was an acute response, which was sustained over time. So, as I said before, we did start the stimulation four weeks after the impulse generator was placed under the clavicle of the patient. At the time of the programming, we were not sure what kind of current was able to treat the symptoms that the patients suffered from. And it was encouraging because a very small electrical current of 0.8V on the right and 1.0V on the left of the substantia nigra pars reticulata were able to acutely treat the hallucinations. And unknown to the patient during the programming, we turned off the stimulation and the patient

was able to report a return of those voices and then of course after we restarted the stimulation, the voices disappeared.

The delusions of paranoia with the patient took a little bit longer to disappear. But after about six weeks after the starting of the stimulation, those were also not present. And now it's more than a year and a half that the patient has received this treatment, which is ongoing, day and night. And she remains symptom-free.

Dr. Wilner:
Wow. So, just to be clear, this is a symptomatic treatment and not a curative therapy, is that right?

Dr. Cascella:
This is true, Dr. Wilner, yes. It's a symptomatic treatment of the positive symptoms that the patient had. We don't know, of course, if the patient will be able to discontinue her current medications. I have to tell the audience that it is encouraging that she was taking 30 mg of haloperidol before the onset of the stimulation and after eighteen months, now, she's down to 10 mg without recurrence of the symptoms. The goal is to eventually discontinue completely the haloperidol and see if she is able to remain symptom-free with just the deep brain stimulation.

Dr. Wilner:
So, Dr. Cascella, what are the next steps? It looks like you've got one big success, what happens next?

Dr. Cascella:
What happens next is we are still looking for the next patient and, your listeners, if they have someone in mind who could benefit from such treatment, can go on a clinicaltrial.gov, find us there, and contact us, and we can eventually screen the subject. We got the approval from the FDA to do this study for three patients with treatment-resistant schizophrenia. It took a while to find the right patient of course and so we are looking for other patients.

I would also like to mention that we are in the process of applying for a grant through NIMH and using the next generation of DBS implant, and this is a system that not only stimulates, but also records and senses the electrophysiology of the brain area that we stimulate. So, the next step will be to eventually record while the patient is on and off of stimulation, while the patient hears hallucinations, and eventually obtain a physiologic biomarker of active hallucinations. By doing that as people are working on the next generation of this type of brain stimulation, called, "closed loop," such that the machine is able to recognize, let's say, a marker of rigidity or excessive tremor in patients, like a beta-band for example, in the STN. So once the machine is able to recognize that there is this beta-band in the STN associated with rigidity, the machine will actively stimulate to eliminate that, to decrease the beta-band and resolve the rigidity. So, in a way, at that point, we will not need the stimulation ongoing night and day, but will intervene at the time when there is, let's say, correlated electrophysiologic marker of these hallucinations and will intervene before the patients experience the hallucination.

Dr. Wilner:
Well, this has certainly been a fascinating look at a potential option for our patients living with treatment-resistant schizophrenia. I want to thank my guest Dr. Nicola Cascella for sharing his recent case study exploring deep brain stimulation. Dr. Cascella, it was a pleasure speaking with you today.

Dr. Cascella:
Thank you very much Dr. Wilner.

Dr. Wilner:
For ReachMD, I'm Dr. Andrew Wilner. To access this and other episodes in our series, visit ReachMD.com/NeuroFrontiers, where you can Be Part of the Knowledge. Thanks for listening.