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Psychotic Symptoms in Parkinson’s Disease Psychosis Disrupts Lives: Early Treatment Intervention Makes a Difference

Announcer:
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Dr. Isaacson:
Hi, I'm Dr. Stuart Isaacson. I'm Director of the Parkinson's Disease and Movement Disorders Center of Boca Raton, in Boca Raton, Florida. And in this segment, we're going to discuss Psychotic Symptoms in Parkinson’s Disrupts Lives: Early Treatment Intervention Makes a Difference.

Parkinson’s disease psychosis is underreported. And this reflects, I think, a couple of different reasons. For one, patients may not know to talk to their treating neurologist or whichever clinician is treating their Parkinson's disease about things that they see that aren't there or things that they hear or feel. They see things, they might go to an ophthalmologist. So patients may be unaware. They may also feel embarrassed. They may have a stigma that they're afraid to talk about, mental health and then problems that they may associate, and they may think they're developing a dementia. For variety of reasons, it may be difficult to elicit a history of Parkinson's psychosis symptoms, such as illusions or sense of passage of presence, hallucinations or delusions. Yet, we know that over 50% of patients who have Parkinson's disease will experience these symptoms over the course of their disease. We have to, therefore, ask about it, to ask about it early, in a non-stigmatizing way. When we ask about constipation and problems sleeping and memory. Do you ever see things that are in there? And if we ask about this, from the beginning of taking care of people with Parkinson's disease, then when these problems do emerge, they’ll probably be more apt to let us know about them, and then we can ask more questions and understand their frequency, their severity, the retention or loss of insight, and try to make treatment decisions.

We know some people are at higher risk of developing Parkinson's psychosis. So we might really key in on these types of people who are of advanced age, who have cognitive impairment or dementia, who have a longer duration or a greater severity of Parkinson's disease, who have sleep disorders, especially REM sleep behavior disorder, with other psychiatric problems like depression, or anxiety, or have visual issues. All these can increase the risk of developing Parkinson's psychosis. Also, some of the medications that we use to treat the motor symptoms or to treat non-motor symptoms like the bladder can also increase the risk of developing a Parkinson's psychosis.

We now understand though that Parkinson's psychosis reflects an underlying degeneration in the brain, a widespread synuclein degeneration that affects not just the dopamine-producing neurons in the substantia nigra, but other neurons and other areas of the brain, including the serotonin neurons and the raphe nuclei and elsewhere. This loss of serotonergic neurons and serotonergic release can lead to an upregulation of serotonin 2A receptors in the cortex and the visual cortex. This can lead we now believe to visual hallucinations, and also increased serotonin 2A receptors that are overactive in the cortex can drive the mesolimbic pathway, the other dopamine pathway, that can lead to hallucinations and delusions.

Understanding Parkinson's psychosis reflects the underlying serotonergic degeneration that's progressive throughout the course of the

disease, helps us understand that the course of Parkinson's psychosis symptoms of hallucinations and delusions is progressive. There's really no such thing as a benign hallucination, because whereas, hallucination when it first emerges, and it may be an illusion first or a sense of passage or presence, we know that this is the beginning of symptoms that will continually begin to increase over time and frequency and severity with loss of insight. This progression tends to occur over months or years, but in one study, it appeared that within 3 years, almost all patients followed, they followed about 48 patients, and 46 out of the 48 progressed to requiring a reduction in dopamine medicines, the addition of an antipsychotic, or worsened symptoms of frequency and severity of hallucinations and delusions.

So we have some evidence base to suggest that even early infrequent or non-severe illusions, hallucinations need to be taken seriously and followed at every visit to see when we have to intervene therapeutically. The reason is that Parkinson's psychosis has a great impact on our patients, on their caregivers, on their families. Stigma and social isolation, impacts also daily activities or quality of life, it disrupts daily life and family life, disrupts getting together and talking, it can be very concerning to someone who sees things that aren't there, or when a loved one sees things that aren't there. We know from a number of studies that caregiver burden is increased in people who have Parkinson's disease with psychosis compared to those without, as well as depression and anxiety.

And Parkinson's psychosis also affects our management of motor symptoms. Because we begin to stop increasing or adding on new dopamine medicines. Indeed, we often begin to lower these, and this leads to suboptimal treatment of motor symptoms, reduced daily activities, quality of life, and in some patients, an increased risks of falls. And also Parkinson's psychosis increases the risk of hospitalization, of prolonging hospitalization, of nursing facility placement, and increases mortality over people with Parkinson's disease alone. Patients who might have a urinary infection stay out of the hospital when they have Parkinson’s psychosis, those symptoms increase and may require hospitalizations. So all these are very important problems that affect our patients and may lead them to enter a nursing facility where they may not leave.

Our current management of Parkinson's psychosis focuses initially on identifying triggers of psychosis, looking at all the medications for both Parkinson's motor and non-motor symptoms, and other medications for other medical conditions looking for anticholinergics, opiates, benzodiazepines, and then looking at some of the dopaminergic medications as well. We want to look for infections and electrolyte disturbances and other medical causes that can bring out more psychosis symptoms. Look at sleep patterns, and other stressors that can occur in daily life.

We think of non-pharmacological therapies like brief psychosocial interventions, redirection and reassurance. And we attempt to evaluate the dopaminergic motor therapies and reduce certain medications that may be more apt to increase psychosis symptoms, like selegiline and amantadine and dopamine agonists. But we don't want to lower the dopamine medicines to impact and worsen motor control, because that's the opposite of what we usually do in treating our patients with Parkinson's disease over the years. So we often have to consider adding an antipsychotic. Only pimavanserin is FDA approved for treating Parkinson's psychosis, the hallucinations and delusions. Off-label use of clozapine, which has been found to have efficacy and two small trials lasting 4 weeks each, can be used. They don't seem to worsen motor Parkinson's but requires intensive blood monitoring for the risk of agranulocytosis that can occur in about 1% of patients. Off-label use of quetiapine can also be used, because it doesn't seem to worsen motor symptoms, but it lacks evidence-based for efficacy. All other antipsychotics should not be used, both by Movement Disorder Society and American Geriatric Society that bears criteria because they will worsen motor Parkinson's.

Pimavanserin was evaluated in a 6-week pivotal trial demonstrating efficacy, safety, and tolerability. Here we can see the improvement that begins both in the placebo and pimavanserin treated groups by 2 weeks, increasing 4 weeks, and we see the maximum effect at 6 weeks, the predetermined primary endpoint, where we see about a 37% improvement in hallucinations and delusions using a validated scale compared to placebo 14%.

In a responder analysis, we can see that about 14% of patients had a full response with resolution of all psychotic symptoms compared to 1% taking placebo. This improvement on the average, a difference between pimavanserin and placebo of over 3 points, can have an improvement in individual patients who may have daily symptoms that impact their daily lives, but after being treated may no longer have daily symptoms. In fact, in a patient with a complete response, they might have complete resolution of all hallucinations and delusions. This, as I said, occurred in 14%.

So I think overall, when we think about Parkinson's disease psychosis nowadays, we recognize that it's underreported by our patients and their caregivers, it’s underdiagnosed, and it’s undertreated. Yet, it's a poor prognostic sign that increases caregiver burden, nursing home placement, hospitalizations, mortality, health-related costs, and it leads to suboptimal treatment of Parkinson's disease motor symptoms. So we think that by asking about this, by recognizing and diagnosing Parkinson's disease sooner, and considering instituting

treatments earlier rather than later, there'll be benefits to our patients and to their caregivers and to their families.

Thank you.

Announcer:
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