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Case Study: Aunt Judy Has Been Hallucinating - Treatment Interventions for Parkinson’s Disease Psychosis

Announcer:
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Dr. Isaacson:
Hi, I’m Dr. Stuart Isaacson, 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 a Case Study: Aunt Judy Has Been Hallucinating – Treatment Interventions.

So Aunt Judy has Parkinson's disease. Her motor symptoms seem to be fairly well controlled when she was seen at an office visit about 8 months ago. She reports she was seeing some things moving in her peripheral vision. When asked about it, she said, ‘Well, you know, I've had these for about 2 years. I haven't really mentioned them, they don't bother me.’ She was taking a levodopa, and then was adjusted to taking 1.5 tablets to the 25/100 strength, 1.5, then 1, 1.5, then 1, on a 4-hour interval, because she was wearing off.

She was seen again 4 months ago, and she notes that slowness and tremor were improved with the adjustment of carbidopa levodopa. But she's now seeing a small squirrel that runs across the TV room two to three times a week. She says she knows the squirrels not real, and that it doesn't bother her. But she also is seeing these things, and it's not really normal to see small rodents running across the living room floor. So we told Aunt Judy and her husband that if they increase in frequency or severity, to give us a call. But like many times we see our patients who begin to have these symptoms, even when they say they're not bothering them, we suggest that perhaps lowering the levodopa a drop to 1.5-1-1-1, lowering it by half the pill. And if she had more motor symptoms, she was asked to call as well.

But it just highlights that we need to really address Parkinson's psychosis symptoms of illusions, a false sense of presence or passage, hallucinations, and delusions by asking about frequency. Is it once a month? Once a week? Once a day? Several times a day. The severity? The insight that's retained or lost? And the impact of these symptoms on daily life on caregivers? And also on motor treatment because it can really pose a therapeutic dilemma when we have to consider whether we have to adjust the motor medicines down when we usually want to raise them up to improve motor symptoms.

We know the course of Parkinson's disease psychosis is progressive, reflecting the progressive neurodegenerative process. We understand Parkinson's psychosis now not to merely reflect a side effect of medications but rather to be an overactive serotonergic system with upregulation of serotonin 2A receptors. And we know that once patients develop symptoms of Parkinson's psychosis, even if they're infrequent and mild, they tend to progress over months and years, and eventually have to be addressed sometimes sooner than later.

When Aunt Judy comes back for an office visit today, she still has motor symptoms, but she's having increasing psychosis symptoms. She reports that she's now seeing squirrels and, at times, birds in her house, several times a day. She's not sure if they're real. She says she's not bothered by the hallucinations, but her husband says that just yesterday, she locked herself in the bedroom all day to quote, keep them away from her. She continues to have off episodes. She has tremor and slowness between doses, and this seems to also be a problem. So we can see with Aunt Judy that she has an increased frequency, she has increased severity. She's lost some insight, and

both the hallucinations keeping her in her room, as well as these off episodes, where she has tremor and slowness, are both impacting her daily life. And they also impact her motor treatment.

So it really highlights that once a patient with Parkinson's disease develop psychosis, they're very different in how we approach and manage the treatment, because now we no longer are just increasing dopaminergic medications to treat motor symptoms, but now we have to sort of try to balance and not increase them too much so that we don't have this other problem of more hallucinations.

This can create a therapeutic bind, where adjusting Parkinson's medications can increase psychosis, and lowering Parkinson's medications can increase motor symptoms. Also, traditionally, thinking about adding an antipsychotic was problematic because all available antipsychotics blocked dopamine receptors, worsening motor Parkinsonism.

With this understanding now that Parkinson's psychosis reflects serotonergic mechanisms, and the generation of serotonergic neurons and loss of serotonin leads to a reflexive upregulation of serotonin 2A receptors, this is progressive. It's sort of a fire burning in the brain. And then dopaminergic medications can add fuel to the fire, as can infections and other medications. So we have to think about Parkinson's psychosis in this neurochemical network type of way. When you have increased serotonergic activity in the visual cortex, you get visual hallucinations. A cortical increase in serotonergic activity can drive the mesolimbic dopamine pathway as well, leading to hallucinations and delusions. It influences and informs our clinical approach to managing patients who develop psychosis when they have Parkinson's disease. Looking for secondary medical causes, medications that might have been added, anticholinergics, opiates, benzodiazepines, looking for infections and electrolyte disturbances. If we don't find triggers like this and looking for other non-pharmacologic triggers, like lack of sleep and anxiety and other stressors that can occur, we're often at a crossroads; we have to decide whether to adjust medications or add an antipsychotic. We're always going to look at the non-Parkinson's medications and minimize anticholinergics and narcotics and such. We'll look at dopaminergic medications and minimize selegiline and amantadine and dopamine agonists, and sometimes lowering other dopaminergic medications. But we don't want to do so and lower those medicines so that patients have more motor symptoms, because that also can considerably impact their quality and daily activities, as well as increasing the risk of falls. So we have to often consider adding an antipsychotic.

Antipsychotics as a class, tend to have efficacy reflecting dopamine D2 blockade and/or serotonin 2A blockade. The problem is with Parkinson's disease patients who are already dopamine depleted, blocking dopamine receptors can really increase motor symptoms. But off-target receptor affinities can also increase non-motor symptoms like somnolence and orthostatic hypotension that our patients already suffer from. And this can be increased by adding an antipsychotic.

Knowledge of the efficacy, if we could look mainly at 2A, like the atypical antipsychotics block 2A in addition to dopamine D2 in this ratio, may give us less dopamine blockade. And targeting just serotonin 2A receptors has the potential to give efficacy as well. Indeed, pimavanserin, which was approved by the FDA, and is the only approved FDA medication for Parkinson's psychosis, selectively blocks serotonin 2A receptors as an antagonist and inverse agonist with a little activity at serotonin 2C receptors, but no affinity for dopaminergic or other receptors that are present. In the pivotal trial, it demonstrated efficacy, safety, and tolerability. At the 6-week primary endpoint, showing a 37% improvement in hallucinations and delusions frequency and severity compared to placebo 14%, without worsening motor symptoms. The UPDRS scale that we used to monitor our patients was unchanged from placebo, and actually showed a direction that would be towards improvement, although not significant.

So Aunt Judy was treated with pimavanserin, 34 milligrams was begun once a day orally with or without food. Her family was told that if she noticed any change in her symptoms, an increase or decrease, any new symptoms to give us a call. We scheduled a follow-up visit for 4 to 6 weeks, and we're going to see efficacy. We maintained the dopaminergic carbidopa levodopa dose, stable right now, and hopefully if we can treat her Parkinson's psychosis, we'll be able to better optimize her motor treatment as well in the future. And hopefully, Aunt Judy will have improvement and with demonstrated tolerability.

So thank you for joining me to discuss this case study of Aunt Judy. And we'll see how she does in 4 to 6 weeks at our follow-up visit. Thanks.

Announcer:
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