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Tavapadon Treatment for Early Parkinson Disease: Findings from the TEMPO Trials

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Becky: Welcome to Practical Neurology: Disease Deep Dive. In this episode, Hubert H. Fernandez, MD, of Cleveland Clinic discusses findings from the TEMPO trials evaluating tavapadone, a selective dopamine D1/D5 receptor partial agonist, as monotherapy in early Parkinson disease and as an adjunct to levodopa in patients with motor fluctuations.

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Joe Rusko: Hello, everyone. I'm Joe Rusko, editor-in-chief of Practical Neurology, and it's my pleasure to chat with Dr. Fernandez today. Dr. Fernandez, please introduce yourself and tell us a little bit about your role at Cleveland Clinic.

[00:00:30]

Hubert H. Fernandez, MD: Yes. I'm Hubert Fernandez. I am a Parkinson disease and movement disorders neurologist, and I direct the Center for Neurological Restoration, which houses the movement disorders program and the Parkinson disease program at Cleveland Clinic.

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Joe Rusko: So tell us a little bit about the TEMPO 2 study, which we saw published in The Lancet Neurology recently.

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Hubert H. Fernandez, MD: This is an exciting time for us. The TEMPO 2 study is one of three pivotal trials of a special compound called tavapadone. It's special because it is a once-daily, D1-selective partial agonist for use as monotherapy and adjunctive therapy in Parkinson disease.

TEMPO 2 is specifically for monotherapy in patients with early Parkinson disease, and it distinguishes itself from TEMPO 1, also a monotherapy study in early Parkinson disease. But TEMPO 1 had a fixed-dose design. Everyone in TEMPO 1 was assigned to placebo, 5 mg, or 15 mg, whereas TEMPO 2 had a flexible-dosing design. Participants were randomized 1:1 to placebo or tavapadone.

And if you were on active treatment with tavapadone, you just had to receive a minimum of 5 mg and a maximum of 15 mg. Whether you needed 5, 10, 15, or somewhere in between was up to the patient and the clinician investigator.

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Joe Rusko: I appreciate that. What were the main outcomes from this study?

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Hubert H. Fernandez, MD: The primary outcome measure of the study is the combined Parkinson motor scores of Parts II and III. Part II is activities of daily living, so it is a subjective scale of how patients function in day-to-day living. Part III is an objective clinical measurement rated by the investigator.

So, the combination of these two—function in activities of daily living and motor severity—is the primary outcome measure. And then, of course, we also check the safety and tolerability of the medication. The really surprising outcome was that the improvement in the combined Parts II and III score among those who received any dose of tavapadone was 10 points higher.

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There was still an improvement in Parts II and III among those who received placebo. Now, this is relevant for us. The minimum clinically important difference between baseline and posttreatment for Part II is really just 1.5 points, and the minimum clinically important difference for Part III is 3 points.

And so, if you score a total difference of 4 or 4.5 points in the combination, you meet the clinical improvement hurdle. We've doubled that in this clinical trial, which is really rare to do. Mainly, very efficacious pills like levodopa are the ones that can do this.

So, the fact that tavapadone can produce this much improvement in efficacy in our patients with early Parkinson disease is remarkable. Now, to be honest with you, we always knew it was a dopamine agonist, and tavapadone's predecessor dopamine agonists are all efficacious. So this follows that trajectory.

And so, it is as good as, if not slightly better than, the older predecessors. But the biggest issue people might have is whether this new dopamine agonist, tavapadone, can achieve that efficacy without the side effects for which its older predecessors are known.

There are idiosyncratic dopamine agonist side effects, such as impulse control behavior disorders, weight gain, sleep attacks or sudden sleep, and a higher propensity for drowsiness, hallucinations, hypotension, and things like that. The intriguing question is whether tavapadone can be as effective in improving motor symptoms without as many side effects as its older predecessors.

We're happy to report that we did not see anything close to the incidence of impulse control behavior disorders, sudden-onset sleep, drowsiness, orthostatic hypotension, or lightheadedness with this medication compared with placebo. Now, the caveat here is that this is a 3-month study.

It was a 3-month study per participant. Of course, the study took a long time because we enrolled 300 patients worldwide, but each patient's exposure in this study was 3 months. A lot of the idiosyncratic side effects of dopamine agonists may appear after 3 months, after chronic exposure.

But at least in the short term, we are encouraged. We are looking forward to the results of the TEMPO 4 study, which is the long-term, open-label study of patients receiving tavapadone. And if we still don't see these side effects after a year of exposure, then we're really onto something special.

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Joe Rusko: That's excellent. So, Dr. Fernandez, I'm wondering if you could tell us a little bit about the adverse events that were more frequent with tavapadone, particularly during titration, and the discontinuations due to adverse events.

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Hubert H. Fernandez, MD: Regarding the tolerability of tavapadone in the TEMPO 2 trial, indeed, we saw a higher incidence of nausea. That was our biggest side effect.

And there were higher discontinuation rates than in other studies, although these couldn't be compared apples to apples. Now, two things about this. One is that any dopaminergic medication can produce what we call generic, or common, dopaminergic side effects.

These are nausea, lightheadedness, and sleepiness, and those are probably the big three. All of the Parkinson medications, including levodopa, rasagiline, COMT inhibitors, and dopamine agonists, can cause them. Now, dopamine agonists might cause a little bit more of these effects than the others, especially drowsiness and orthostatic hypotension.

The good news here is that tavapadone doesn't cause as much drowsiness as we thought and doesn't cause as much orthostatic hypotension. It does a little, but not as much. But it did cause a lot of nausea. That's one consideration. The second is that the incidence of nausea and the incidence of dropouts are about the drug, sure, but they're also about the clinical trial design.

When we design a study, we have to blend what is feasible and what is ideal. Ideally, we would take all the time in the world to slowly ramp up patients to a tolerable dose, right? But if we do that, it'll run forever, and it'll be very expensive. So we have to shorten the titration period to a reasonable level that patients can tolerate and the study budget can accommodate.

In the real world, doctors and patients don't have to follow such a rigid titration. They can take their time. I follow the titration as a guide, but if my patient says, 'Doc, I'm still nauseated,' we would stay at that dose until they're used to it before moving to the next level.

In the clinical trial, you have no choice. Whether or not you're doing well, you're going up to the next level, and then whether or not you're doing well, you're going up to the next level. Therefore, the nausea incidence could be artificially high because of the forced titration. Regarding the discontinuation rate, if you don't reach at least 5 mg, you're going to be out of the study.

So, it was an automatic discontinuation. If you don't comply with certain requirements or you miss a dose here and there, that's an

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automatic discontinuation. Believe it or not, this study was also taking place during the COVID years. This study withstood COVID.

This study withstood the Russia–Ukraine war. And guess what? We had sites in Ukraine, and every site had COVID patients. They developed COVID. They weren't getting shipments because of logistical barriers from the war. They would drop out because they would not have been compliant with the medication.

We had to close down some sites because it was literally impossible to ship medications, especially to those in Ukraine. So the discontinuation rate is a reflection, to some extent, of the drug, but also of the study design.

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Joe Rusko: Thank you for that context. That's very helpful. What about TEMPO 2 in relation to the TEMPO 3 trial? Do you want to briefly mention how that's part of this whole picture?

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Hubert H. Fernandez, MD: Yeah. The other special thing about tavapadone is that it is one of the few drugs studied in both early Parkinson disease and moderate to advanced Parkinson disease. Most of the drugs currently marketed are approved for one or the other, not both.

So, the potential broad-spectrum indication of tavapadone is particularly interesting to us. TEMPO 3 is the pivotal trial of tavapadone as an add-on therapy to levodopa among patients who are not getting the full benefit of levodopa and are experiencing what we call motor fluctuations.

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Joe Rusko: Excellent. I want you to speculate: Where do you see this fitting into the overall treatment armamentarium?

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Hubert H. Fernandez, MD: At a minimum, the entry of tavapadone provides yet another option for a newly diagnosed patient with Parkinson disease. A newly diagnosed patient, starting from ground zero, may not be suffering from severe motor symptoms.

Not all of them will require levodopa, and levodopa is also a medication taken at least 3 times daily. So in, say, a younger patient with milder motor symptoms and a busy lifestyle, once-daily tavapadone could tide them over for even 2 or 3 years before starting a medication taken 3 times a day.

At a minimum, it provides an option for newly diagnosed patients with Parkinson disease. My best guess is that as clinicians get a feel for how efficacious this medication is and how to use it, they will first use it in younger patients with milder disease. As they become more familiar and confident with the effects and tolerability of tavapadone, they may slowly begin to use it in older patients and those with more severe disease.

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Joe Rusko: Excellent. Any final comments?

[00:14:30]

Hubert H. Fernandez, MD: My final comment is that neurologists were traumatized by the incidence of impulse control behavior disorders.

It is traumatic to the patient and the clinician when, all of a sudden, a patient uses up their life savings because of pathological gambling or becomes involved in sexual solicitations and whatnot. It is rare, but its impact is of significant consequence if it does happen.

It did occur at a higher incidence with dopamine agonists. So not many of us are using the older-generation dopamine agonists now because of that fear. But I just want to remind the audience that hypersexuality, pathological gambling, and impulse control behavior disorders have been described with levodopa and with other dopaminergic compounds, although they occur at a higher incidence with dopamine agonists.

So, I expect that, in a best-case scenario for tavapadone, there might be one or two patients who develop this, but it doesn't mean this drug follows the trajectory of its older predecessors. After all, levodopa can do this, rasagiline can do this, and other dopaminergic medications can do this. So we have to be vigilant, for sure, but we also have to keep the context and not say, with our first patient who develops a hint of an impulse control behavior disorder, 'Oh, this is no good.'

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Joe Rusko: I think no drug is exempt from that. That's an important point you brought out, so thank you for that. I just want to say thank you for your time today.

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Hubert H. Fernandez, MD: You're welcome.

[00:16:23]

Becky: Thank you to Dr. Fernandez for his insights, and thanks to you, our listeners. This podcast is brought to you by the editors of Practical Neurology. Be sure to visit practicalneurology.com for more podcasts in the field of neurology.

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