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Exploration of an Evidence-Based Treatment Option for Convulsive Seizures in Your Patients With Epilepsy

Announcer Introduction:
Welcome to ReachMD. This medical industry feature, titled "Exploration of an Evidence-Based Treatment Option for Convulsive Seizures in Your Patients With Epilepsy" is sponsored by Eisai Incorporated.

Here's your host, Dr Jennifer Caudle.

Dr Caudle:
An estimated 3.4 million people in the United States have epilepsy,[1] and approximately 1.6 million of them predominantly experience convulsive seizures.[2]

The ability to control convulsive seizures is influenced by many different treatment-related factors, such as adverse side effects associated with an antiseizure medication[3] and adherence.[4] Today we'll discuss a specific treatment for the reduction of convulsive seizures in the pursuit of seizure freedom: FYCOMPA® (perampanel), a schedule III controlled substance.

This is ReachMD and I'm your host, Dr Jennifer Caudle. Joining me to discuss the use of FYCOMPA in his clinical practice is Dr Julio Cantero, a neurologist specializing in epilepsy. Dr Cantero, thanks for being here today. Would you please tell us a bit about your practice?

Dr Cantero:
Of course. My practice in Sarasota, Florida, is part of a multispecialty group. About one-third of the patients I see have epilepsy, and of that third, about 70% have refractory epilepsy. In addition to working in my practice, I also teach at the medical school at Florida State University.

Dr Caudle:
Thank you, Dr Cantero.

Also joining us is Dr David King-Stephens, an adult epilepsy specialist. Dr King-Stephens, please tell us a bit about your practice.

Dr King-Stephens:
Sure. I work at a Level 4 epilepsy program at Yale University, and about 70% of the patients I treat have refractory epilepsy. The other 30% of patients are either newly diagnosed or have easy-to-control epilepsy.

Dr Caudle:
Thank you both. I'm glad you could join us today.

When you think about the patients you see in your practice, what do they hope to get out of treatment? And do their goals align with yours?

Dr King-Stephens, why don't you start us off?

Dr King-Stephens:
Absolutely. As a physician, my goal is to control the seizures while minimizing side effects, and whether that's achievable or not depends on many factors.

Given that I work at an Epilepsy Center and deal with refractory seizures, which are defined as failure to respond to at least 2 antiseizure medication trials, the goal of seizure freedom is not always possible to achieve. We are referral centered, and we tend to see a very refractory groups of patients, meaning that they've tried several medications but continue to have disabling seizures. I would say that patients*do* share our goal of controlling seizures and limiting side effects.

Dr Caudle:
Thank you, Dr King-Stephens. Dr Cantero, same question to you.

Dr Cantero:
Well, you know, we have expectations as physicians and epileptologists, and patients have their own expectations.

So in each particular case, we have to educate the patient on what can be achieved and then come to an agreement.

Dr Caudle:
Now, Where does convulsive seizure freedom fit in to your goals, Dr Cantero?

Dr Cantero:
Well, ideally our goal is seizure freedom. But remember: We see a lot of patients whose epilepsy is what we call*intractable*, so that's when we know they likely won't be seizure free. For these patients, we aim for reduction or control of the most significant seizures.

We also see other patients who are newly diagnosed and have tried only 1 medication, and those patients could have a good chance of achieving seizure freedom.[5]

Dr Caudle:
Thank you, Dr Cantero. Dr King-Stephens, what are your thoughts on this?

Dr King-Stephens:
I agree that the goal would ideally be convulsive seizure freedom, but we know that many patients with refractory epilepsy are just looking to control their most disabling seizures. And improved control is really important, because these disabling seizures are associated with increased morbidity and mortality.[6,7]

But we really do have so many approaches that we can use, including antiseizure medications—like FYCOMPA. It is indicated for several patient populations and can be used as monotherapy for the treatment of partial-onset seizures, as first-adjunctive therapy, or as a later add-on.[8]

Dr Caudle:
Thank you both. Your responses really set us up nicely to discuss FYCOMPA and its clinical studies in different patient populations. Dr Cantero, would you remind our listeners about FYCOMPA and its indication?

Dr Cantero:
Absolutely. FYCOMPA is the first and only noncompetitive AMPA-receptor antagonist antiseizure medication.

It's indicated in patients with epilepsy aged 4 years and older for partial-onset seizures with or without secondarily generalized seizures. It's also indicated as adjunctive therapy for patients aged 12 years and older for primary generalized tonic-clonic seizures.[8]

FYCOMPA targets the activity of glutamate, the primary excitatory neurotransmitter in the central nervous system, at postsynaptic AMPA receptors.[8,9] FYCOMPA is thought to reduce excitatory neurotransmission, although the precise mechanism by which FYCOMPA exerts its antiepileptic effects in humans is unknown.[8]

Dr Caudle:
And Dr King-Stephens, would you please remind our listeners of the Boxed WARNING in FYCOMPA's label?

Dr King-Stephens:
Sure. FYCOMPA has a Boxed WARNING for serious psychiatric and behavioral reactions.

Serious or life-threatening psychiatric and behavioral adverse reactions, including aggression, hostility, irritability, anger, and homicidal ideation and threats, have been reported in patients taking FYCOMPA, irrespective of prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression.

Monitor patients for these reactions as well as for changes in mood, behavior, or personality that are not typical for the patient, particularly during the titration period and at higher doses.

FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening.

I would ask our listeners to please note that more important safety information for FYCOMPA will be provided throughout this podcast, and to please refer to the full prescribing information for FYCOMPA, as well.

Dr Caudle:
Thank you, Dr King-Stephens. So when you're starting a patient on FYCOMPA, how do you counsel them on the Boxed WARNING? And what other safety and tolerability information do you think is important to share?

Dr King-Stephens:
So, we talk about the potential common side effects and the serious side effects that can happen, such as sedation and dizziness.

I do go over the data related to the Boxed WARNING about serious psychiatric and behavioral reactions, I explain the number of cases in which homicidal ideation was reported, and I tell the patient and their caregivers to report any change in mood as soon as it happens, so that we can establish whether it could be the medication and whether we need to reduce the dose or discontinue the treatment.

Dr Caudle:
Dr Cantero, is that consistent with how you approach safety with your patients?

Dr Cantero:
Yes, I would agree. The important part is to remember to start low and go up slowly. And that's what we all do in practice. That way, we have time to adjust. And patients themselves have time to adjust. If bothersome side effects remain, then we can work on adjusting dosing.

Dr Caudle:
Now, there were 3 randomized, double-blind, placebo-controlled, Phase III clinical trials of FYCOMPA for partial-onset seizures.[8]

Dr King-Stephens, would you give us an overview of the study design?

Dr King-Stephens:
Sure. So, the 3 trials were identical in design, apart from the doses studied and the study sites. These were prospective, double-blind, placebo-controlled add-on trials in refractory groups of patients with partial-onset seizures.[8]

In all, 1478 patients aged 12 years or older were included in the trials. Patients enrolled had inadequate seizure control and were receiving 1 to 3 concomitant antiepileptic drugs, or AEDs.[8,10-12] During the trials, more than 85% of patients were taking 2 to 3 concomitant AEDs, and approximately 50% were on at least 1 AED known to induce CYP3A4, resulting in a significant reduction in FYCOMPA's serum concentration.[8]

Studies 1 and 2 compared 8-mg and 12-mg once-daily doses of FYCOMPA to placebo, whereas Study 3 compared 2-mg, 4-mg, and 8-mg doses to placebo.[8,12]

Dr Caudle:
Moving to you, Dr Cantero, please tell our listeners about the primary endpoint data from these trials?

Dr Cantero:
The primary endpoint in all 3 trials was percent change in seizure frequency per 28 days during the treatment period compared to the baseline period.[8]

A statistically significant decrease in seizure rate was observed at doses of 4 mg to 12 mg per day, and dose response was apparent at 4 mg to 8 mg per day, with little additional reduction in frequency at 12 mg per day.[8]

Dr Caudle:
Dr Cantero, what can you tell us about the safety profile seen in these trials?

Dr Cantero:
In the partial-onset seizure trials, there were 1038 patients who received FYCOMPA at doses of 2 mg, 4 mg, 8 mg, or 12 mg once daily, and this was the safety population in the pooled analysis of the 3 pivotal partial-onset seizure trials.[8]

Adverse reactions occurring in at least 5% of partial-onset seizure patients on FYCOMPA 4, 8, or 12 mg and with at least 1% higher frequency than in the placebo group were dizziness, somnolence, headache, irritability, fatigue, falls, ataxia, nausea, vertigo, back pain,

and balance disorder.[8]

Dr Caudle:
Thank you for that clear overview. Now that we've reviewed the pivotal trial, Dr Cantero, how do you incorporate FYCOMPA into your practice?

Dr Cantero:
Most patients we see have some indications for the medication. And because FYCOMPA has been studied as monotherapy for partial-onset seizures,[13] I can consider this option for many of my patients. So pretty quickly, it has become one of the first medications that can be used.

Another characteristic of FYCOMPA is its long half-life.[8] If for some reason a patient doesn't remember to take the medication at night as directed, that factor is important. He or she should resume dosing the following day at the prescribed daily dose. Patients also should be instructed to contact their health care provider if more than 1 day of dosing is missed.[8]

Dr Caudle:
Okay, great. Dr King-Stephens, how has FYCOMPA been integrated into your practice?

Dr King-Stephens:
In my practice, it's a bit different because of the referral pattern that we have. Typically, I see patients who have received other medications. So it becomes easy to suggest, "Well, because you haven't tried a medication with this MOA, it's worth giving it a shot while we also determine whether you would be candidate for a surgical or other treatment."

Also, for epilepsy, it's critical that people remember to take their medication every day because, especially for drugs that have a short half-life, missing a dose can result in a reduction in the serum level that puts them outside the therapeutic window.

Because of that, having a drug with a long half-life, like Dr Cantero said, may be something to consider for some patients.

Dr Cantero:
I'd like to add that, at nighttime, if patients create a connection between the habit of taking their pill and another habit, like brushing their teeth or going to bed—something like that, it might be easier for patients to remember to take the medication.

Dr King-Stephen:
That's a great point, Dr Cantero.

Dr Caudle:
Wonderful insights from both of you. Now I'd like to circle back to something that Dr Cantero brought up, which is the use of FYCOMPA as monotherapy for the treatment of partial-onset seizures. That brings us to the FREEDOM study.

This study was a 26-week maintenance, open-label monotherapy study of newly diagnosed or untreated patients with partial-onset seizures.[13]

Dr Cantero, would you provide an overview of the study design?

Dr Cantero:
Sure. The primary study objective was to evaluate the seizure-freedom rate during a 26-week maintenance period of the study.[13]

All patients were between the ages of 12 and 74 years and had a clinical diagnosis of epilepsy with partial-onset seizures with or without secondarily generalized seizures.[13]

A total of 73 patients, 96% of whom were newly diagnosed with epilepsy, entered the 4-mg maintenance period and had at least 1 post-dose primary efficacy measurement.[13,14]

During the 6-week titration period, patients initiated FYCOMPA 2 mg once daily for 2 weeks and then were uptitrated to FYCOMPA 4 mg once daily for 4 weeks. And if no safety issues were noted, patients entered the 26-week 4-mg maintenance phase.[13]

If a patient experienced a seizure during the 26-week 4-mg maintenance phase, the patient was titrated to FYCOMPA 6 mg once daily for 2 weeks followed by 8 mg once daily at the discretion of the investigator.[13]

Dr Caudle:
Dr King-Stephens, would you please tell us about the primary endpoint and adverse events in the FREEDOM trial?

Dr King-Stephens:
Of course. Of the 73 patients with partial-onset seizures who entered the 26-week maintenance period, 63% were seizure free on 4 mg per day at Week 26. Twenty-one patients were not controlled on 4 mg and were titrated up to 8 mg per day.[13]

Of the 48 patients who entered the 26-week 4-mg maintenance period and had partial-onset seizures with secondary generalization, nearly two-thirds were free from convulsive seizures at Week 26 of the maintenance period.[13]

This study has some limitations. The study design was open label and did not include a control arm; appropriate multiplicity adjustments were not applied; and the information is descriptive.[14]

Dizziness was the most frequent adverse reaction for patients receiving FYCOMPA 4 mg per day, reported in 26.5% of these patients. Additional adverse reactions reported by at least 10% of patients receiving FYCOMPA 4 mg once daily were somnolence, nasopharyngitis, and headache.[13]

Dr Caudle:
Thank you both. Now I'd like to put this trial data into context for our listeners.

Dr Cantero, do you have a patient case that comes to mind that can illustrate the use of FYCOMPA in the first-line setting?

Dr Cantero:
Yes, I do. I have a patient whom I see regularly now.

To give a little background, she had been in a car accident. She was going to make a left at an intersection, and then the next thing she knew, she had crashed against a construction barrier. She damaged the car and she didn't know what had happened. We tested her, and she met criteria for the diagnosis of focal left temporal lobe epilepsy. This was her first incident, so she was not taking any medications.

This patient is in her 50s, is very active, and works. I proposed a medication that she can take at night when she goes to bed. And, of course, we started at the low-dose. We know that some patients with partial-onset seizures may respond to 4 mg daily.[8] She was placed initially on 2 mg once daily. About 6 months ago, she came in, and we went up to 4 mg once daily. She hasn't had any further seizures.

Of course, each patient may respond differently, and it's important to monitor tolerability and efficacy throughout the course of treatment.

Dr Caudle:
That's anexcellent case example, Dr Cantero. Let's follow the same framework for discussing FYCOMPA as first-adjunctive treatment for partial-onset seizures, which was studied in the FAME trial.

Dr King-Stephens, would you provide a high-level overview of this study?

Dr King-Stephens:
No problem. The FAME study was a 24-week maintenance, multicenter, open-label, Phase IV prospective study of FYCOMPA as first-adjunctive therapy after AED monotherapy failure in patients ages 12 and up with partial-onset seizures, with or without secondarily generalized tonic-clonic seizures. Patients whose seizures were not controlled with monotherapy were started on FYCOMPA 2 mg per day once daily at bedtime.[15]

Throughout the 12-week titration period, the daily FYCOMPA dose was increased incrementally by 2 mg per day at intervals of at least 2 weeks and titrated up or down depending on clinical response and tolerability.[15]

Patients then took a maintenance dose ranging from 4 mg per day to 12 mg per day throughout the entire 24-week maintenance period.[15]

Among the 85 patients in the full analysis set, 80% achieved a reduction in partial-onset seizures of at least 50%—the primary endpoint for the study. And nearly half of patients, 47%, experienced seizure freedom.[15]

Of particular note, among the 16 patients with convulsive seizures, 87.5% experienced a reduction of at least 50% in convulsive seizure frequency. Three-quarters of these patients experienced convulsive seizure freedom at 6 months.[15]

This study also had some limitations. This study was open-label and did not include a control arm. Appropriate multiplicity adjustments were not applied, and this information is only descriptive. In addition, the study included a relatively small number of patients.[14]

Of the 102 patients in the FAME study's safety set, 75.5% reported treatment-emergent adverse events.[15]

The most common treatment-emergent adverse events were dizziness, somnolence, and headache.[14]

Dr Caudle:
Thank you, Dr King-Stephens, for that in-depth overview.

Dr Cantero, do you have an example of a patient who received FYCOMPA as first-adjunctive therapy that you could share?

Dr Cantero:
The first patient who comes to mind was on his usual work commute from Sarasota to Tampa when he noticed that his arm was shaking and he couldn't control the car, and he crashed.

He was taken to the hospital after the collision, and at the hospital he was found to have a frontal meningioma. So, he had surgery for the meningioma. It was resected, and then he was placed on a generic first-line antiseizure medication at the hospital. The dose was increased over time, and then he had a couple of convulsions.

So that day when he crashed, he actually went into a convulsion. He had had a focal seizure followed by a lateral generalization, bilaterally spread. They treated him for focal epilepsy with secondary generalization, but he continued to have convulsions, which is when he came to see me.

I didn't discontinue the other medication, but I added FYCOMPA. I started him with 2 mg of FYCOMPA and went up to 4 mg at the next appointment, and he has been on that dose since.

It's been more than a year now, and he hasn't had any seizures since starting the adjunctive FYCOMPA. And again, although this particular patient did not experience adverse effects with FYCOMPA, it's important to monitor tolerability and efficacy over the treatment course.

Dr Caudle:
I have 1 more question before we wrap up our discussion. Dr King-Stephens, will you remind our listeners of the Important Safety Information for FYCOMPA?

Dr King-Stephens:
Sure. FYCOMPA's Important Safety Information provides additional information around the Boxed WARNING. In the partial-onset seizures clinical trials, hostility- and aggression-related adverse reactions occurred in 12% and 20% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 6% of patients in the placebo group. These effects were dose-related and generally appeared within the first 6 weeks of treatment, although new events continued to be observed through more than 37 weeks. These effects led to dose reduction, interruption, and discontinuation.

The combination of alcohol and FYCOMPA significantly worsened mood and increased anger. Patients should avoid the use of alcohol.

Patients, their caregivers, and families should be informed that FYCOMPA may increase the risk of psychiatric events.

Patients should be monitored during treatment with FYCOMPA, especially when taking higher doses.

It is also important to discuss the Important Safety Information about Suicidal Behavior and Ideation.

Antiepileptic drugs, including FYCOMPA, increase the risk of suicidal thoughts or behavior in patients.

Patients, their caregivers, and families should be informed of the risk and advised to monitor and immediately report the emergence or worsening of depression, suicidal thoughts or behavior, thoughts about self-harm and/or any unusual changes in mood or behavior.

FYCOMPA caused dose-related increases in events related to dizziness and disturbance in gait or coordination, especially during the titration phase.

FYCOMPA caused dose-dependent increases in somnolence and fatigue-related events, especially during the titration phase.

Patients should be advised against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of FYCOMPA is known.

Patients should be carefully observed for signs of central nervous system (CNS) depression when FYCOMPA is used with other drugs with sedative properties because of potential additive effects.

Falls were more common in patients taking FYCOMPA at doses of 8 mg and 12 mg versus placebo.

Drug reaction with eosinophilia and systemic symptoms, also known as multiorgan hypersensitivity, has been reported in patients taking AEDs, including FYCOMPA. DRESS may be fatal or life-threatening.

Evaluate your patients if these signs or symptoms are present.

A gradual withdrawal is generally recommended with AEDs to minimize the potential of increased seizure frequency.

The most common adverse reactions include dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, headache, vomiting, contusion, abdominal pain, and anxiety.

FYCOMPA may decrease the efficacy of contraceptives containing levonorgestrel.

Plasma levels of FYCOMPA were decreased when administered with moderate and strong CYP3A4 inducers.

FYCOMPA may enhance the effects of alcohol on vigilance, alertness, anger, confusion, and depression.

These effects may also be seen when FYCOMPA is used in combination with other CNS depressants.

Caution should be exercised when FYCOMPA is administered to pregnant or nursing women.

Use in patients with severe hepatic or severe renal impairment is not recommended.

Dosage adjustments are recommended in patients with mild or moderate hepatic impairment.

Use with caution in patients with moderate renal impairment.

And finally, FYCOMPA is a Schedule III controlled substance and has the potential to be abused and lead to drug dependence and withdrawal symptoms.

Dr Caudle:
That's some great information for us to think about as we come to the end of today's program. I'd like to thank my guests, Dr Julio Cantero and Dr David King-Stephens, for helping us better understand the use of FYCOMPA to treat convulsive seizures.

It was great speaking with you both today.

I'm your host Dr. Jennifer Caudle. Thanks for listening.

Announcer Close:
This program was sponsored by Eisai Incorporated. If you missed any part of this discussion, visit ReachMD.com/industryfeature. This is ReachMD. Be Part of the Knowledge.

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