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Partial-Onset Seizures: New Data & Experts' Real-World Experience with an AED

Dr. Najm:

This is Reach MD, and I'm Dr. Imad Najm, and joining me today are Dr. Matthew Holtzman, a neurologist from Wayne, Michigan, Dr. Joanne Rogin, Medical Director for the Midwest Center for Seizure Disorders in Minneapolis, Minnesota, and Advanced Practice Registered Nurse and Certified Nurse Practitioner, Lucretia Long, who is a clinical assistant professor of neurology at the Ohio State University in Columbus, Ohio. Regardless of how much training and education you receive on new treatment options, applying them in a real-world setting can be challenging. And treating partial-onset seizures is no exception. We have a panel of experts here with us to share our own real-world experiences treating patients with newly diagnosed or untreated partial-onset seizures, and specifically a treatment option that you may not have previously considered for these patients. We will also be discussing some monotherapy seizure freedom data for newly diagnosed or untreated patients with partial-onset seizures. A big thanks to all of you for joining me today.

So, starting with you, Dr. Holtzman, what are the characteristics we should look for in an antiepileptic medication for patients with newly diagnosed or untreated partial-onset seizures with secondarily generalization?

Dr. Holtzman:

Well, that's a really great question. First, in my practice, seizure freedom is the gold standard for treatment in convulsive seizures. So, convulsive seizures, as we know, are the most dangerous kinds of seizures. They have a high risk for injury, and there's a social stigma attached to them, especially if they happen in public. It can be embarrassing, they can get very injured by it. There can be an emergency room cost. So for me, seizure freedom is really critical. And finally, I'm looking for a medication that's going to have a very low treatment burden, specifically once-a-day dosing.

Dr. Najm:

From my standpoint, in my clinic, we do not aim for just seizure control. Our goal, whenever it's possible, is complete seizure freedom. Therefore, the chosen AED should also have a well-understood safety profile. Personally, I also prefer AEDs with long half-life because plasma levels remain relatively stable in the event of a missed dose. And we all know how many times our patients miss a dose here and there.

I think it's quite important that we always counsel our patients who we suspect are missing doses of their antiepileptic medication. Ms. Long, how do you counsel patients who you suspect are missing doses of their antiepileptic medications?

Ms. Long:

So I think that's a very important component of comprehensive care. In my practice, I tend to highlight the risk of missing doses; advise them to set alarms on their phone, work with patients and caregivers to address non-adherence, and also reduce treatment burden when possible by using a once-a-day medication regimen.

Dr. Rogin:

I also think this is very important. And so I ask my patients at each visit not just whether they've missed a dose, but how many doses they've missed, and which doses they're missing. And then work on strategies. And the things that I recommend are also weekly pill boxes, setting a phone alarm—I will sometimes ask the caregiver in their presence to become involved.

Dr. Najm:

Thank you very much, Dr. Rogin.

Let's now take a look at the potential treatment option for newly diagnosed or untreated partial-onset seizures, perampanel. Now, it's important to keep in mind that perampanel is indicated in patients with epilepsy aged 4 years and older for partial-onset seizures with or without secondarily generalized seizures. Perampanel is also indicated as adjunctive therapy for patients aged 12 years and older for primary generalized tonic-clonic seizures. Please stay tuned for additional important safety information, including the complete boxed warning relating to serious or life-threatening psychiatric and behavioral adverse reactions.

How did you become comfortable using perampanel, particularly for your newly diagnosed or untreated patients with partial-onset seizures? Let's start with you, Ms. Long. I know you do not see newly diagnosed patients, but how did you become comfortable using perampanel?

Ms. Long:

Well, initially I was hesitant to utilize FYCOMPA because of the boxed warning; however, as I gained experience with it, initially with intractable patients, I became more and more comfortable using it earlier in my practice. Now with the new Freedom data, which we will discuss a little later, along with my experience using FYCOMPA in the clinic, and from my initial experience, I would strongly consider using it in a newly diagnosed or untreated patient. Indeed, I'm currently using it earlier in my practice.

Dr. Rogin:

For me, I became experienced with FYCOMPA during the clinical trials. My experience using it in the trials in my tough-to-treat intractable patients there helped me become more comfortable with using FYCOMPA in my general practice. I now use it in newly diagnosed partial-onset seizures, and in my new-onset partial-onset seizure patients, and as early adjunctive and partial-onset seizures.

Dr. Holtzman:

Well, in my experience, I initially used FYCOMPA in my refractory patients. But as I used FYCOMPA and became more comfortable using it, I began to move it up in my regimen. I was very happy when FYCOMPA received its monotherapy indication because I like to prescribe patients one drug with once-daily dosing. I also saw that some of my partial-onset patients did not need to go up to the 8 to 12-mg dosing, and were responding to 4 mg.

Dr. Najm:

Thank you, Dr. Holtzman. Like you, Dr. Holtzman, in my experience, I have seen that some of my partial-onset seizure patients with secondarily generalization responded to 4 mg of perampanel.

In my opinion, the new FREEDOM study may be of interest for healthcare professionals who are not yet comfortable utilizing perampanel in newly diagnosed or untreated patients. Dr. Holtzman, can you take us through the FREEDOM study?

Dr. Holtzman:

I sure can. The Freedom study is a 26-week open-label study of FYCOMPA monotherapy in newly diagnosed or untreated patients with partial-onset seizures with or without secondary generalization. The objective of this study was to evaluate the seizure freedom rate during the 26-week maintenance phase in untreated patients with partial-onset seizures. The evaluation criteria focused on the efficacy and safety of FYCOMPA when used as monotherapy in new-onset, newly diagnosed, or untreated patients with partial-onset seizures, including secondarily generalized seizures. In this study, 96% of the patients were newly diagnosed with epilepsy. These patients presented with the seizure types seen here. The majority of patients presented with complex partial seizures with secondary generalization. Seventy three patients entered the 4-mg maintenance period, and had at least one post-dose primary efficacy measurement. These patients had experienced a median baseline seizure frequency of two seizures per 12 weeks. Following a 28-day pre-treatment phase, patients were started on 2 mg of FYCOMPA for two weeks, and then titrated to 4 mg of FYCOMPA for 4 weeks. They then began a 26-week maintenance phase, during which they were monitored for seizure freedom. If a seizure occurred during this 26-weeks maintenance phase, patients were titrated to 6 mg once daily, and then 8 mg once daily. During the 26-week maintenance phase, the majority of the newly diagnosed or untreated patients with partial-onset seizures were convulsive seizure free. In the open-label analysis, 63% of patients with partial-onset seizures achieved seizure freedom with FYCOMPA 4 mg. Of the patients with secondarily generalized seizures at baseline, 65% achieved seizure freedom. Now, it's important to note that this was an open-label study without blinding or randomization or control arm. Appropriate multiplicity adjustments were not applied, and the information presented here is descriptive. The adverse events at 26 weeks that occurred in at least 5% of patients taking 4 mg of FYCOMPA included dizziness at 26.5%, somnolence at 13.2%, nasal pharyngitis at 13.2%, and headache at 10.3%. Psychiatric adverse reactions

reported during the 4-mg treatment phase of the Freedom study include irritability, affect lability, depression, and insomnia. It's important to note that of the 22 patients who discontinued treatment during the 4-mg treatment phase, 8 patients were 9% discontinued due to an adverse event. Additional reasons for discontinuation include subject choice, inadequate therapeutic effect, lost to follow-up, or withdrawal of consent, and other.

Dr. Najm:

Thank you, Dr. Holtzman. I think we can all agree that we all are pleased to see perampanel monotherapy seizure freedom data for patients with newly diagnosed partial-onset seizures, including those with convulsive seizures.

Dr. Holtzman, previously you mentioned that you consider efficacy, safety, and treatment burden when you choose an antiepileptic medication for the newly diagnosed or untreated patients with partial-onset seizures.

Dr. Holtzman:

For me, FYCOMPA checks off all of those boxes because of new monotherapy seizure data in the Freedom trial, as well as my own experience with newly diagnosed or untreated patients with partial-onset seizures. A safety profile that I am familiar with, and has been well established across several studies, and once again of course once-daily dosing.

Ms. Long:

So, while I don't see newly diagnosed patients, I agree with Dr. Holtzman. In particular, FYCOMPA's Freedom data on seizure freedom at 4 mg reinforces how I utilize FYCOMPA in my practice, and is another reason why I'm very comfortable using FYCOMPA earlier rather than later in my patients in whom I do use FYCOMPA. I've also been starting patients on FYCOMPA 2 mg and titrating on two-week intervals, while targeting lower doses. I like the fact that it's once daily. And I also think that the 105-hour half-life is a highlight of FYCOMPA.

Dr. Najm:

In my personal practice, starting at 2 mg and stopping to assess at 4 mg allows me to get an initial evaluation of the antiepileptic medication with the patient. I think our key takeaway is that some patients with partial-onset seizures may respond to perampanel 4 mg, so when using perampanel in new-onset patients, we may want to pause and assess at the 4-mg dose. Recommended maintenance dose range is 8 to 12 mg once daily for patients with partial-onset seizures, although some patients may respond at 4 mg. It is important to also note that, in children, perampanel is dosed the same as it is in adolescents and adults; no weight-based dosing is required.

I know that all of us have patients who miss doses of their medication. Dr. Rogin, can you tell us about the half-life of perampanel, and what effect that has when a patient misses a dose?

Dr. Rogin:

Sure, happy to.

As you may know, FYCOMPA has a long half-life of up to 105 hours based on a model of 4-mg daily treatment over a period of 4 weeks. The long half-life of FYCOMPA was established in Phase 1 clinical trials with healthy adults. The time to maximum serum concentration, or T-Max, of FYCOMPA ranges between 0.5 to 2.5 hours in fasting conditions. Steady state is achieved in about 2 to 3 weeks. FYCOMPA is dosed once daily. It's important to allow sufficient time to evaluate the effect of any dose changes. Considering the long half-life of FYCOMPA, it's important to understand how missed doses affect the steady-state plasma concentrations.

A pharmacokinetic model was constructed to explore this and look at the effects of a missed dose on FYCOMPA steady-state plasma concentrations. Pharmacokinetic simulations were for adult patients receiving 8 mg of FYCOMPA. And the pharmacokinetic parameters were derived from data from 19 Phase 1 FYCOMPA trials, and this included a total of 606 patients. Please note that the results of this study are limited because the pharmacokinetic model is based on simulations and not on prospective clinical studies in humans, so further studies are needed to replicate the findings. So, looking at the graph, in these simulated concentration time profiles, which are based upon 8-mg daily dosing in adults, FYCOMPA will remain relatively stable throughout the dosing interval due to its long half-life. The graph on the left demonstrates modeled FYCOMPA plasma exposure in a patient who is not on a concomitant enzyme-inducing antiepileptic drug. And who has missed a dose at Day 15, and then resumed that regular dosing the following day. On Day 15, we see the trough concentration decline by 18%, and the peak concentration decline by 12%. Within six to seven days of the missed dose, modeled FYCOMPA exposure was very close to that of a patient who did not miss a dose.

The graph on the right demonstrates modeled FYCOMPA plasma exposure in a patient on concomitant carbamazepine, an enzyme inducer, who has missed a dose of FYCOMPA at Day 15, and resumed regular dosing the following day. On Day 15, the trough

concentration declined by 44%, and the peak concentration declined by 15%. Within three to four days of missed dose, modeled FYCOMPA exposure was very close to that of a patient who did not miss a dose. Remember that per prescribing information, FYCOMPA should be administered once daily at bedtime. Patients who miss a dose, should resume dosing the following day at their prescribed dose. So, we instruct patients to contact their physician if more than one day of dosing is missed.

Dr. Najm:

Thank you, Dr. Rogin. And turning to you now, Dr. Holtzman, earlier you mentioned that safety profile is an important consideration for you when you choose an antiepileptic drug for your patients with new-onset, partial-onset seizures. So, with this in mind, could you review the important safety information for perampanel?

Dr. Holtzman:

This is information I always discuss with my patients when initiating FYCOMPA.

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.

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 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. 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 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 reactions with eosinophilia and systemic symptoms, also known as multiorgan hypersensitivity, have 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 perampanel 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.

FYCOMPA is a Schedule III controlled substance and has the potential to be abused and lead to drug dependence and withdrawal symptoms. Please see the Full Prescribing Information for FYCOMPA, including the Boxed Warning regarding SERIOUS

PSYCHIATRIC AND BEHAVIORAL REACTIONS, or visit FYCOMPA.com/hcp.

Dr. Najm

Thank you for reviewing that, Dr. Holtzman. And just from my own perspective, I think a key takeaway from our discussion is that some patients may respond to perampanel 4 mg. So when using perampanel in newly diagnosed or untreated patients with partial-onset seizures, we may want to pause and assess at the 4-mg dose. But unfortunately, that's all the time we have today. So, in closing, I want to thank you, Dr. Holtzman, Dr. Rogin, and Ms. Long, for helping us better understand the use of perampanel in patients with newly diagnosed or untreated partial-onset convulsive seizures.

Please see some of the related links below the player for more information about perampanel. It was great speaking with all of you today.