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Centanafadine for Management of Executive Dysfunction and Emotional Dysregulation in Children and Adolescents with ADHD

Announcer:

You're listening to ReachMD. This program titled "Centanafadine for Management of Executive Dysfunction and Emotional Dysregulation in Children and Adolescents with ADHD," is sponsored by Otsuka America Pharmaceutical Inc.

This program will discuss the results of post-hoc analyses that evaluated the effectiveness of centanafadine, which is a first-in-class norepinephrine, dopamine, and serotonin reuptake inhibitor, or NDSRI, and CNS stimulant in addressing associated features, including executive dysfunction and emotional dysregulation in adults with ADHD.

Dr. Greg Mattingly is a paid consultant of Otsuka America Pharmaceutical Inc.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:

Welcome to ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me today is Dr. Greg Mattingly to discuss the results of post-hoc analyses looking into the effectiveness of centanafadine.

Dr. Mattingly is a physician and principal investigator in clinical trials for Midwest Research Group, as well as the founding partner of St. Charles Psychiatric Associates in Weldon Spring, Missouri, and past president of the American Professional Society of ADHD and Related Disorders, or APSARD. Dr. Mattingly, welcome to the program.

Dr. Mattingly:

Great to be here with you.

Dr. Caudle:

I'd like to start with some background on ADHD's complex clinical presentation. So, Dr. Mattingly, how common are associated features like executive dysfunction and emotional dysregulation in these patients?

Dr. Mattingly:

Dr. Caudle, as you and many of our audience may know, ADHD is a chronic neurodevelopmental disorder that affects children, adolescents, and adults.¹

What may be less known is that ADHD is more than just those 18 core symptoms, those symptoms that address areas of inattention, hyperactivity, and impulsivity, and that, by definition, those symptoms have to be causing impairment in multiple domains of our patients' lives. If we think about where those levels of impairment come in, it's quite often due to associated features and common comorbidities.¹

So executive function difficulties may be as common as core symptoms in our children and adolescents with ADHD.²⁻⁴ We also know that approximately half of children and two-thirds of adults with ADHD will have difficulties with underlying emotional regulation.^{5,6}

Some of the clinical manifestations of each of these would be, for executive function problems, things like working memory, and working memory can be difficulty with time management, forgetting instructions, losing items, losing my train of thought.^{1,2,4,7-11}

So it can be the child who gets their homework done but forgets to bring it to class. It can be the adult who runs late. They say, "I have a sense of time blindness where my internal clock just doesn't work the way it should," or losing my train of thought, where I derail and am unable to finish a project that I started.

Another aspect of executive function includes task initiation and management, so that ability to shift from a preferred to a non-preferred task.^{1,2,4,8-11} That could be coming in after work and having to sit down and pay the bills. That could be a child who has to come in off the playground and sit down and start studying. So the ability to start up a topic or switch from one task to another. Quite often, that can lead to issues around procrastination. So procrastination, putting off a non-preferred task, having a difficulty staying with a preferred task can certainly be difficult for our individuals with ADHD.^{1,2,4,8-11}

Another aspect of ADHD can be what we call inhibitory control.^{1,2,4,7-11} So executive function can affect the ability to inhibit my behaviors, so interrupting or blurting out, interrupting someone in the middle of a conversation, blurting out something that comes to my mind. Top of mind doesn't mean top of mouth. Or impulsive actions such as impulsive spending, impulsive intimacy, impulsive eating, difficulties with stopping behaviors where I get started and I have a difficulty with inhibiting my behaviors once they had started.

Some of the common manifestations of difficulties with emotional regulation would be things like emotional lability—, getting frustrated, having abrupt mood shifts, dropping into sudden sadness, dysphoria, agitation in response to a trigger.^{1,5,6,12-15}

My patients will tell me, "Listen, I know everyone gets frustrated by it, but my brain clicks. My brain just goes from zero to a hundred. I get frustrated all of a sudden, I get moody, I get irritable, and it's hard for my brain to modulate those aspects of my emotions." For many of my patients, this can spill over into irritability. They say, "Listen, in response to stress, in response to a trigger, I just tend to blow." One of my adult patients said, "Listen, I've learned to manage it at work. It used to be a difficulty when I was a child, but now at work I do okay. It's coming home from work where I get frustrated in traffic, I get frustrated with my family. I come home with my hair on fire. Little things trigger me. I get anger. I have rapid emotional shifts. Those can be verbal outbursts and sometimes they can be physical outbursts with my family."

Emotional reactivity can sometimes bleed into another associated feature, and that is rejection sensitivity.¹⁵ Being hypersensitive to criticism, having strong responses to minor triggers, having impulsive outbursts followed by regret, low self-esteem, getting in my own head, having difficulties with relationships, and becoming self-critical as a result of rejections and perceived resentments.^{13,15}

Duration of recovery can also be a key issue. We know that many of our patients with ADHD can become triggered very quickly in response to a frustration, but sometimes it also affects their ability to self-soothe, self-modulate that frustration. So difficulty calming down where I find myself left in the sense of being at unease, dysregulated, being frustrated, having a prolonged emotional response, and hanging onto anger and resentment that I know I should be letting go of.^{12,14,15}

Dr. Caudle:

That was very helpful and so descriptive. I really appreciate it as a family doctor. You know, when it comes to addressing executive dysfunction and emotional dysregulation, where do you see gaps in traditional approaches to ADHD management?

Dr. Mattingly:

Dr. Caudle, I think we all use medications for what they were designed for, and traditional ADHD medicines were designed to help various aspects of those core symptoms of ADHD, but they may not target all aspects of ADHD or the associated neurobiology. Traditional ADHD medicines were designed to target dopamine and/or norepinephrine, but they did not address serotonin and may not fully address some of these associated features with ADHD.^{1,16-19}

When we talk to patients, less than 30 percent report full satisfaction with their current ADHD stimulant treatments.²⁰ So we see that the majority say there's still unmet needs even being treated with a standard ADHD treatment.

40 to 60 percent do not experience improvements in those associated features when treated with traditional ADHD medicines.^{16,18,21}

So when we ask patients about ADHD, they'll say, you know, between a third to two-thirds, thirty to sixty-one percent will say, "Listen, I still have residual symptoms with what we call executive function. I have difficulties prioritizing. I have difficulties organizing."

Some of my patients will describe a sense of time blindness. "I'm always running late for things. I don't mean to, but then I get overwhelmed. I know I've got too much on my plate. My mind just doesn't have a good internal clock."^{19,22-24}

Another 45 percent of individuals say, "I have ongoing symptoms of emotional difficulties, emotional regulation," despite being treated with an ADHD treatment.¹⁶

Dr. Caudle:

Well, why don't we take a closer look at the new pharmacologic treatment option for ADHD. What can you tell us about centanafadine and its mechanism of action?

Dr. Mattingly:

Centanafadine is a first-in-class norepinephrine, dopamine, and serotonin reuptake inhibitor. We call it a NDSRI, it's a triple reuptake inhibitor, not just for norepinephrine and dopamine, but also for serotonin. While the exact mechanism of action for any medication, including centanafadine, is somewhat unknown in the treatment of ADHD, the pharmacodynamics are characterized by selective inhibition of norepinephrine, dopamine, and serotonin reuptake transporters.²⁵⁻²⁸

Centanafadine has been investigated, and I've been proud to be a part of a number of these investigations across four phase 3 clinical trials and three long-term open label trials.²⁹⁻³¹

It's important to know that centanafadine has been approved by the FDA for treatment of children, adolescents, and adults with underlying ADHD.^{28,32}

Dr. Caudle:

For those of you who are just tuning in, you're listening to ReachMD. I'm Dr. Jennifer Caudle, and today I'm speaking with Dr. Greg Mattingly about the potential role of centanafadine in addressing the associated features of ADHD.

Now, a recent post-hoc analysis evaluated the effect of centanafadine on executive dysfunction and emotional dysregulation in children and adolescents. What should we know about the two phase 3 clinical trials pooled into this analysis?

Dr. Mattingly:

We took data from two phase 3 trials, looking at children in one, another one in adolescents.^{29,30} And we said, "Let's take that data together and try to ask some questions that weren't asked in the original pivotal trials." The primary endpoint in both of these phase 3 trials was the change in core ADHD symptoms, the ADHDRS-5, which measures the 18 symptoms of core ADHD.^{29,30,33,34}

This pooled analysis, which included both studies, one in children and one in adolescents, said, "We want to take a look at the effect of centanafadine on associated features in a population with impairments in either executive function or impairments in emotional regulation."^{33,34}

The definition of populations with impairments in executive function and emotional regulation came to us through a common rating scale. It's a scale that's been used by teachers, clinicians, and schools across America for decades, called the Conners Rating Scale.^{29,30,33,34}

The Conners Rating Scale not only measures ADHD symptoms but it also has sub-domains that look at executive function. In the Conners Rating Scale, a patient who has a content score of 70 or more is considered to have very high levels of executive function difficulties.³⁴

Similarly, on the Conners Rating Scale, we can plot a sub-domain that looks at emotional regulation. Patients that have an elevated score of greater than 70 on the defiant aggression content are also considered to have high levels, very elevated levels of emotional difficulties or emotional dysregulation.³³

Some of the limitations. This was a post hoc analysis where we combined two of the pivotal trials. It was not controlled for multiplicity, and these questions were answered after the original pivotal trials had been completed. We wanted to take a look at emotional regulation, emotional dysfunction, and executive regulation, executive dysfunction, and these were assessed by the Conners Parent Short Form, a form that was filled out by parents about how are your children doing.

And this scale is obviously a holistic scale that looks at ADHD symptoms with sub-domains that looks at executive function and emotional regulation. It is not a specific scale specifically designed to capture individual items specifically of any of these specific symptoms.^{33,34}

Dr. Caudle:

Now, let's turn to the findings of this post-hoc analysis. How did centanafadine perform in children and adolescents with impairments in executive function?

Dr. Mattingly:

So if we take a look at the effects of centanafadine on core symptoms in patients who had high levels of impairments in executive function as assessed by the Conners 3 rating scale, we saw that centanafadine had improvement on aspects of ADHD symptoms.³⁴

But more importantly, improvement on aspects of executive function or executive dysfunction in our patients. So we take a look at defiance and aggression and learning problems in patients with impairments of executive function. We saw that centanafadine had

improvement in these symptom domains.³⁴

Dr. Caudle:

And what did the data look like for children and adolescents with impairments in emotional regulation?

Dr. Mattingly:

When we take a look at children and adolescents who had difficulties with emotional regulation, we saw that the effect of centanafadine on core symptoms with these impairments improved their symptoms of ADHD and improved their overall aspects of ADHD in these associative features.³³

In this post-hoc analysis, the effect of centanafadine on defiance and aggression, executive function difficulties, and learning problems and impairments in emotional regulation were all improved with centanafadine.³³

Dr. Caudle:

So, Dr. Mattingly, if we shift over to the safety data, what were the most common treatment-emergent adverse events in the study?

Dr. Mattingly:

The most common adverse events were consistent, both in the group that had high levels of executive function difficulties and in the group that had difficulties with emotional regulation.^{33,34}

Discontinuation due to adverse events in the children and adolescents with impairments in executive function or difficulties with emotional regulation were the same for both subpopulations. 7.6 percent of children and adolescents discontinued the medication due to adverse events, with centanafadine versus one percent for those on placebo.

Dr. Caudle:

Taken together, what do these results suggest in terms of addressing executive dysfunction and emotional dysregulation with centanafadine in children and adolescents?

Dr. Mattingly:

That this post hoc analysis answers a very important clinical question, both for clinicians and for the patients for whom we care.

Centanafadine showed the potential to address not only the core symptoms of ADHD, but also improved issues with executive function and difficulties with emotional regulation in children and adolescents struggling with ADHD.^{33,34}

Dr. Caudle:

So given everything we've talked about today, Dr. Mattingly, how can recognition of executive dysfunction and emotional dysregulation in ADHD influence our treatment decisions?

Dr. Mattingly:

It's important to step back and look beyond the core symptoms of ADHD, those 18 symptoms that make the diagnosis, but think about the broad aspect about ADHD and how it presents in our offices and in our patients' lives.^{1,17,18}

In my experience, executive function and emotional dysregulation are frequently quite often harder to treat. So when we take a look at those symptoms, we'll see that they tend to be quite often missed, they tend to sometimes be forgotten, and quite often they can be the residual issues that are causing impairment in my patients' lives.

Dr. Caudle:

Well, that's a great way to round out our discussion, and I'd like to thank my guest, Dr. Greg Mattingly, for helping us better understand approaches to managing executive dysfunction and emotional dysregulation in ADHD. Dr. Mattingly, it was great speaking with you today.

Dr. Mattingly:

Wonderful to be here. Thank you.

Dr. Caudle:

Of course. And for ReachMD, I'm your host, Dr. Jennifer Caudle. And before we close, let's take a moment to review some important safety information for centanafadine.

Announcer:

INDICATION and IMPORTANT SAFETY INFORMATION for SIMTRIYO® (centanafadine)

INDICATION

Simtriyo is a norepinephrine-dopamine-serotonin reuptake inhibitor and central nervous system stimulant indicated for the treatment of ADHD in adults and pediatric patients 6 years of age and older weighing at least 20 kilograms.

Limitations of Use

The use of Simtriyo is not recommended in pediatric patients younger than 6 years of age, because this pediatric subpopulation had a higher incidence of weight loss than pediatric patients 6 years of age and older, or in pediatric patients weighing less than 20 kilograms, because of a lack of data for this subpopulation and the risk of weight loss.

IMPORTANT SAFETY INFORMATION

WARNING: SUICIDAL IDEATION AND BEHAVIORS IN PEDIATRIC PATIENTS AGED 6 YEARS AND OLDER

Higher rates of suicidal ideation and behaviors occurred in Simtriyo-treated patients aged 6 to 12 years with attention-deficit/hyperactivity disorder (ADHD) than in placebo-treated patients. Closely monitor all pediatric patients for suicidal ideation and behaviors. Consider stopping Simtriyo in patients who experience emergent suicidal ideation and behavior.

WARNING: ABUSE, MISUSE, AND ADDICTION

Simtriyo has a potential for abuse and misuse. Abuse of central nervous system (CNS) stimulants, including Simtriyo, can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including Simtriyo, can result in overdose and death. Before prescribing Simtriyo, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of Simtriyo, and proper disposal of any unused drug. Throughout treatment, reassess each patient's risk and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

Contraindications: Simtriyo is contraindicated in patients with a known hypersensitivity to centanafadine or any of the excipients of Simtriyo, taking or within 14 days of stopping a monoamine oxidase inhibitor, or with pheochromocytoma or a history of pheochromocytoma.

Risks to Patients with Serious Cardiac Disease: Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease.

Increased Blood Pressure and Heart Rate: Assess heart rate and blood pressure following increases in dosage, and periodically while on therapy.

Psychiatric Adverse Reactions: If new psychotic or manic symptoms occur, consider discontinuing Simtriyo.

Hypersensitivity Reactions: Serious hypersensitivity, including anaphylaxis and angioedema, have been reported. If a clinically significant hypersensitivity reaction occurs, immediately discontinue Simtriyo and initiate appropriate therapy.

Long-Term Suppression of Growth in Pediatric Patients: Closely monitor height, body mass index and linear growth in pediatric patients. Consider treatment interruption in patients not growing or gaining height or weight as expected.

Peripheral Vasculopathy Including Raynaud's Phenomenon: Carefully assess for digital changes during Simtriyo treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy.

Serotonin Syndrome: Use of Simtriyo with other serotonergic drugs may cause serotonin syndrome. If occurs, discontinue Simtriyo and/or concomitant serotonergic drug.

Motor and Verbal Tics and Worsening of Tourette's Syndrome: Regularly monitor patients for the emergence or worsening of tics or Tourette's syndrome. Discontinue Simtriyo if clinically appropriate.

Most commonly observed adverse reactions (≥5% and greater than placebo): The most common adverse reactions in pediatric patients (aged 6 to 12 years) were rash and decreased appetite, and (aged 13 to 17 years) decreased appetite, nausea, rash, headache, and abdominal pain. The most common adverse reactions in adults were headache, decreased appetite, insomnia, nausea, dry mouth, and diarrhea.

Pregnant women exposed to Simtriyo and healthcare providers are encouraged to contact the National Pregnancy Registry for ADHD Medications at 1-866-961-2388 or visiting <https://womensmentalhealth.org/research/pregnancyregistry/adhd-medications/>

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA1088 (www.fda.gov/medwatch).

Please see FULL PRESCRIBING INFORMATION, including **BOXED WARNINGS**.

This program was sponsored by Otsuka America Pharmaceutical, Inc. If you missed any part of this discussion, visit ReachMD.com, where you can Be Part of the Knowledge.

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