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

Announcer:
You're listening to ReachMD. This program, titled "Centanafadine for Management of Executive Dysfunction and Emotional Dysregulation in Adults 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. Joel Young is a paid consultant of Otsuka America Pharmaceutical Inc.

Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to ReachMD. I'm Dr. Charles Turck.

Joining me for this conversation is Dr. Joel Young. He's the founder and medical director of the Rochester Center for Behavioral Medicine and an associate clinical professor of psychiatry and family medicine at Wayne State University in Detroit, Michigan. Dr. Young, we're so glad to have you here.

Dr. Young:
Well, thanks. It's great to be here.

Dr. Turck:
Now, before we dive into the data, let's talk about the complexity of ADHD clinical presentation. Dr. Young, how commonly do associated features like executive dysfunction and emotional dysregulation present alongside core symptoms of ADHD?

Dr. Young:
Well, let me first say that ADHD is a chronic neurodevelopmental disorder affecting both children and adults. But ADHD is more than the diagnostic core symptoms of inattention, hyperactivity, and impulsivity. It's also characterized by associated features and common comorbidities.[1] Executive dysfunction may be as common as the core symptoms of inattention, hyperactivity, and impulsivity in children and adults with ADHD.[2-4] Approximately half of children and two-thirds of adults with ADHD have emotional dysregulation.[5,6]

Let's talk about the clinical manifestations of executive dysfunction. These include impaired working memory. These patients have difficulty with time management. They often complain to me that they forget instructions. They often leave things behind. They lose their train of thought. They also tell me that they have difficulty starting tasks and managing or switching tasks. They often procrastinate, and that's a very significant problem. They also have impaired inhibitory control, which can look like interrupting or blurting out impulsive actions, including spending or actually difficulty stopping behaviors.[1-4,7-10]

Let's switch to the clinical manifestations of emotional dysregulation. These include emotional lability, which can look like frustration, abrupt mood shifts, and sudden sadness or dysphoria. It's evident that these patients can be irritable. They can be easily annoyed or angered. They have rapid emotional shifts and verbal outbursts, and they also have emotional reactivity, and sometimes they have rejection sensitivity, and this is manifest by hypersensitivity to criticism or strong responses to even minor triggers. They can have impulsive outbursts followed by regret or even low self-esteem. And then we see delayed recovery. They have trouble calming down.

They have prolonged emotional responses, and they hold on to their anger.[1,5,6,11-14]

Dr. Turck:
And building on that, what limitations do you see with traditional management strategies when it comes to addressing executive dysfunction and emotional dysregulation in ADHD?

Dr. Young:
Well, traditional ADHD medicines do not target all aspects of ADHD neurobiology like dopamine, norepinephrine, and serotonin, and they may not fully address associated features in ADHD, again, beyond the core symptoms.[1,15-18]

So as it stands, less than thirty percent of individuals treated for ADHD report full satisfaction with their current stimulant therapy,[19] and forty to sixty percent do not experience improvements with the associated features, the emotional dysregulation, the executive dysfunction, when they're treated with traditional ADHD medications.[15,17,20] Over half of these patients do not report that residual symptoms of executive dysfunction and emotional dysregulation are well addressed.[15,18,21-23]

Dr. Turck:
So given that clinical context, this is a great transition into our discussion of centanafadine. Would you walk us through the mechanism of action behind this compound?

Dr. Young:
I sure will. Centanafadine is a first-in-class norepinephrine, dopamine, and serotonin reuptake inhibitor. It's an NDSRI. That will be a new concept.[24] The mechanism in the treatment of ADHD is unclear, but efficacy could be mediated through its activity as an NDSRI.[24-27] Now, centanafadine has been investigated across four phase three clinical trials and two long-term open-label trials,[24,28-30] and centanafadine has been approved by the Food and Drug Administration for the treatment of ADHD in children, adolescents, and adults.[24,31]

Dr. Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Joel Young about the potential role of centanafadine in ADHD management. So that brings us to the pooled post-hoc analysis of the phase three trials evaluating centanafadine and its effects on core symptoms, as well as executive dysfunction and emotional dysregulation in adults.

Dr. Young, would you tell us about the trials that were included in this analysis?

Dr. Young:
In the study design, there were two identically designed phase III trials. The primary endpoint of the two phase III trials was change from baseline at day 42 in the Adult ADHD Investigator Symptom Rating Scale total score, the ASRS. [24,30,32] These analyses assessed the effect of centanafadine on core symptoms and executive dysfunction and emotional regulation using the Adult ADHD Self-Report Scale, the ASRS.[32] Now, the study limitations are important. This was a post hoc analysis, and it did not control for multiplicity.[32]

Dr. Turck:
Now with that in mind, what did the results of this post-hoc analysis reveal about centanafadine's effects on core symptoms and associated features in adults with ADHD?

Dr. Young:
Well, centanafadine was associated with improvements from baseline to week six in the ASRS 18 total score, and this suggests that the subjective experience of adults with ADHD correspond to the clinician-related improvements in ADHD using the AISRS. And this was the primary endpoint in the two phase III clinical trials.[32] Centanafadine was also associated with improvements across the ASRS subscales, which assessed these core symptoms of hyperactivity, impulsivity, and inattention.[32] In addition, centanafadine was associated with improvements in the ASRS subscale for executive dysfunction in week six in adults with ADHD as assessed by the ASRS expanded version.[33] Improvements were observed across individual ASRS executive function scales, and these include items like time management, planning, prioritization, starting tasks and completing those tasks, working memory-related difficulties as well.[33] Centanafadine was associated with improvements in the ASRS subscale for emotional dysregulation at week six in adults with ADHD, and this was assessed by the ASRS expanded version.[34] Now, improvements were also associated and observed across individual ASRS emotional dysregulation, including those related to affective lability, emotional overactivity, and anger outbursts.[34]

Dr. Turck:
And what do the phase three results tell us about the safety profile of centanafadine in adults?

Dr. Young:
Well, most treatment emergent adverse events were considered mild or moderate in adults who received centanafadine.[30] We look at the discontinuation rates. So due to treatment emergent adverse events, they were 6.2 percent for centanafadine at four hundred milligrams and 4.8 percent at centanafadine two hundred milligrams. This compares to one point four percent on placebo.[24,30]

Dr. Turck:
So looking at the data as a whole, what would you say are the key takeaways about treating executive dysfunction and emotional dysregulation with centanafadine in adults?

Dr. Young:
Well, in this post hoc analysis, centanafadine showed potential to address not only core symptoms, but also executive dysfunction and emotional dysregulation in adults with ADHD. These are important features that are often misidentified, and we here see the potential to address these additional symptoms.[30,32]

Dr. Turck:
And before we wrap up today, Dr. Young, let's think big picture. How can earlier recognition of associated features like executive dysfunction and emotional dysregulation inform management of ADHD?

Dr. Young:
Well, the need to assess ADHD beyond these core symptoms of inattention and hyperactivity, impulsivity, we need to look beyond these core symptoms for more comprehensive treatment planning and addressing broad ADHD symptoms.[16,17] So in my experience, having done this for a while, executive dysfunction and emotional dysregulation are hard to detect and frequently hard to treat.

Dr. Turck:
Great comment for us to think on as we come to the end of today's program. And I want to thank my guest, Dr. Joel Young, for helping us understand how we can better address the wide range of symptoms in ADHD. Dr. Young, it was wonderful speaking with you today.

Dr. Young:
Dr. Turck, it was great speaking with you as well.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. Please stay tuned to hear some important safety information.

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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