Highly Effective Gene Therapies for SMA: Where Do We Go From Here?

BY ELIZABETH A. KICHULA, MD, PHD; AND JOHN F. BRANDSEMA, MD

Pediatric Sleep Disorders: Assessment and Treatment

BY YOLANDA A. YU, DO; AND ALON Y. AVIDAN, MD, MPH

Potential Therapeutic Role of the Endocannabinoid System for Migraine

BY JENNIFER S. SUN, PHD

Perspectives From the Journey of the Patient With Rare Epilepsy

FEATURING JOSEPH E. SULLIVAN, MD; KELLY KNUPP, MD; MARY ANNE MESKIS; AND TRACY DIXON-SALAZAR, PHD

Coverage of the Consortium of Multiple Sclerosis Centers Annual Meeting

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Trudhesa is an ergotamine derivative indicated for the acute treatment of migraine with or without aura in adults.

WARNING: PERIPHERAL ISCHEMIA FOLLOWING COADMINISTRATION WITH POTENT CYP3A4 INHIBITORS
Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of dihydroergotamine with strong CYP3A4 inhibitors. Because CYP3A4 inhibition elevates the serum levels of dihydroergotamine, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of Trudhesa with strong CYP3A4 inhibitors is contraindicated.

Limitations of Use
Trudhesa is not indicated for the preventive treatment of migraine or for the management of hemiplegic or basilar migraine.

Contraindications
Trudhesa is not recommended in patients with:
- Concomitant use of strong CYP3A4 inhibitors such as protease inhibitors (eg, ritonavir, nelfinavir, or indinavir) and macrolide antibiotics (eg, erythromycin or clarithromycin)
- Ischemic heart disease or coronary artery vasospasm
- Uncontrolled hypertension, known peripheral arterial diseases, sepsis, following vascular surgery, or severe hepatic or renal impairment
- Hypersensitivity to ergot alkaloids
- Concomitant use of other 5-HT₁ agonists (eg, sumatriptan) or ergotamine-containing or ergot-type medications within 24 hours
- Concomitant use of peripheral and central vasoconstrictors

Warnings and Precautions
Trudhesa may cause:
- Cardiac events: Cardiac events in patients with risk factors of coronary artery diseases. Consider administration of the first dose of Trudhesa under medical supervision (including the use of an electrocardiogram)
- Cerebrovascular events: Cerebrovascular events (eg, cerebral hemorrhage, subarachnoid hemorrhage, and stroke) have been reported, particularly with dihydroergotamine mesylate injection
- Vasospasm/elevated blood pressure: Dihydroergotamine may cause vasospasm or elevation in blood pressure
- Fibrotic complications: Rare cases have been reported following prolonged daily use of dihydroergotamine mesylate. Administration of Trudhesa should not exceed the dosing guidelines or be used for chronic daily administration
- Medication overuse headache: Detoxification may be necessary
- Preterm labor: Advise pregnant women of the risk
- Local irritation: Local irritation has been reported following administration of Trudhesa

Most Common Adverse Reactions
Most common adverse reactions (incidence >1%) were rhinitis, nausea, altered sense of taste, application site reactions, dizziness, vomiting, somnolence, pharyngitis, and diarrhea.

Use in Special Populations
Pregnancy: Available data from published literature indicate an increased risk of preterm delivery with Trudhesa use during pregnancy.
Lactation: Patients should not breastfeed during treatment with Trudhesa and for 3 days after the last dose.

Please see the Trudhesa Full Prescribing Information, including Boxed Warning and Medication Guide.

The risk information provided here is not comprehensive. The FDA-approved product labeling can be found at www.trudhesaHCP.com or 1-800-555-DRUG. You can also call 1-833-TRUDHESA (1-833-878-3437) for additional information.

DHE=dihydroergotamine mesylate.

References:
12 Highly Effective Gene Therapies for SMA: Where Do We Go From Here?

BY ELIZABETH A. KICHULA, MD, PhD, AND JOHN F. BRANDSEMA, MD

DEPARTMENTS

PUBLISHER’S NOTE

ENTERING A NEW ERA OF MEDICINE

FROM THE EDITOR

SHIFTING THE PARADIGM: EARLIER USE OF ON-DEMAND THERAPY FOR TREATING OFF TIME IN PARKINSON DISEASE

IN THE HEADLINES

FDA ADVISORY COMMITTEE IS SET TO RECONVENE ON ALS TREATMENT

FDA ACCEPTS ALZHEIMER DISEASE TREATMENT APPLICATION

MEDICAL WORLD NEWS®

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PLASMA NEUROFILAMENT LEVEL IS CORRELATED WITH SYMBOL DIGIT MODALITY SCORES FOLLOWING OZANIMOD TREATMENT

WOMEN WITH MS USE SOCIAL MEDIA TO DISCUSS SAFETY CONCERNS ON DMT USE IN PREGNANCY

10 MAGNIMS SCORE PREDICTS RISK OF DISABILITY DETERIORATION OVER TIME

16 POTENTIAL THERAPEUTIC ROLE OF THE ENDOCANNABINOID SYSTEM FOR MIGRAINE

BY JENNIFER S. SUN, PHD

CURE CONNECTIONS®

27 PXT3003 AIMS TO BECOME FIRST APPROVED THERAPEUTIC FOR CHARCOT-MARIE-TOOTH DISEASE

SLEEP MEDICINE

28 PEDIATRIC SLEEP DISORDERS: ASSESSMENT AND TREATMENT

BY YOLANDA A. YU, DO, AND ALON Y. AVIDAN, MD, MPH

FEATURES

NEUROPATHWAYS®

PERSPECTIVES FROM THE JOURNEY OF THE PATIENT WITH RARE EPILEPSY

FEATURING JOSEPH E. SULLIVAN, MD; KELLY KNUPP, MD; MARY ANNE MESKIS; AND TRACY DIXON-SALAZAR, PHD

CLINICAL TRIAL FOCUS

11 DMT USE IN PREGNANCY TO DISCUSS SAFETY CONCERNS

33 PEOPLE IN THE NEWS

SUBSCRIBE to our e-newsletter. Get the latest breaking news, specialty coverage and conference coverage straight to your inbox at NeurologyLive.com.
Entering a New Era of Medicine

THE GOAL OF TREATMENT FOR many fields of medicine has been achieving personalized medicine. For those who specialize in the care of individuals with chronic neurologic conditions, this is no different. These patient populations are often quite heterogeneous, sometimes with refractory diseases, resulting in a need for a variation in both treatment and care team approaches. Fortunately, the multidisciplinary care model has been adopted by many institutions across the country, leading to a better focus on comprehensive, holistic care. And for neuromuscular disorder specialists, such as those who care for spinal muscular atrophy (SMA), the treatment paradigm has entered a new era of genetic medicine— inching closer to that ultimate goal.

August is recognized annually as SMA Awareness Month, and in honor of that, this issue of NeurologyLive’s cover story, on page 12, focuses on the progress that has been made in the management of this disease. Authored by Elizabeth A. Kichula, MD, PhD, and John F. Brandsema, MD, the story provides an overview of the 3 available genetically targeted treatments, explores some of the questions that their introduction has spurred, such as the potential of combination approaches, and offers a look to the future of this new therapeutic age.

Neuromuscular medicine cannot be discussed without the mention of the pediatric patient population that is so often affected by these disorders. Although, in the public eye, this population can be sometimes overlooked among individuals with other neurologic diseases. One such group that is sometimes less frequently discussed is children and adolescents with sleep disorders. As such, on page 28, Alon Y. Avidan, MD, MPH, and Yolanda A. Yu, DO, offer an overview of the landscape of pediatric sleep disorders and their first-line treatment strategies. The scientific understanding of sleep and sleep processes overall has evolved dramatically in a short period, and as more continues to be discovered, the possibilities for patients with sleep disorders have similarly improved.

Another area of recent scientific progress has been in migraine. With a number of investigational agents making their way through the clinical development pipeline and to patients, the future treatment armamentarium of headache disorders appears bright. Featured within these pages is a deep dive into a mechanistic target that might have the potential to grow physicians’ treatment resources further: the endocannabinoid system. On page 16, Jennifer S. Sun, PhD, offers an overview of the system and its budding promise as a therapeutic aim for migraine in the coming years.

As we strive to keep you abreast of the latest research and tools to improve your clinical practice, we always welcome your feedback. If you have any comments or thoughts about our coverage or would like to contribute to NeurologyLive, please email Managing Editor Matt Hoffman at mhoffman@neurologylive.com.
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Shifting the Paradigm: Earlier Use of On-Demand Therapy for Treating OFF Time in Parkinson Disease

By Daniel Kremens, MD, JD

WITH THE INTRODUCTION OF TRIPTANS in the 1990s, the treatment of migraine was revolutionized. No longer did patients have to suffer with acute migraine attacks that occurred despite the use of prophylactic medications because triptans could safely and reliably abort those breakthrough migraines. Neurologists and primary care physicians now routinely use on-demand therapies to treat migraine. Despite the availability of safe and effective medications to relieve OFF episodes in Parkinson disease (PD), we have not seen similar widespread adoption of these on-demand therapies. It is time to shift the treatment paradigm in PD.

More than 50 years since its introduction, oral levodopa (typically combined with a dopamine decarboxylase inhibitor) remains the gold standard for the treatment of PD’s motor symptoms. Despite the remarkable benefits of levodopa, more than half of patients will develop motor complications including OFF time within 5 years of starting the drug. OFF time is defined as that time when a medication no longer provides its expected benefit and motor and nonmotor signs reemerge.

OFF periods can have a significant impact on the quality of life of patients and their caregivers. Patients will limit their activities and avoid social situations because of concerns about OFF episodes. They leave their homes less frequently, and often only if accompanied by their caregivers. As a result, caregivers are also limited in their ability to leave the home and must be prepared to return if the patient experiences an OFF episode. Patients report difficulty with communication during OFF periods, which leads them to avoid interacting with others.

It is believed that OFF time is the result of both central and peripheral mechanisms. Centrally, PD is characterized by the loss of dopaminergic neurons that synthesize, store, and release dopamine. As those cells die, patients lose their “buffering” capacity for exogenous levodopa, and wearing off emerges. Peripherally, gastrointestinal (GI) dysfunction contributes to OFF episodes. PD is associated with delayed gastric emptying. Oral levodopa is absorbed only in the duodenum and proximal jejunum of the small intestines, and delayed gastric emptying can result in loss of the benefit of an oral levodopa dose. Similarly, dietary protein in food competes with levodopa for absorption through the large neutral amino acid transporters in the gut and at the blood-brain barrier. Small intestine bacteria overgrowth and Helicobacter pylori infections have also been implicated in dose failures.

OFF time typically is treated by using higher doses or longer-acting formulations of carbidopa levodopa. This, however, has been associated with worsening OFF episodes in the long term. Adding adjunctive therapies, including dopamine agonists, monoamine oxidase inhibitors, COMT inhibitors, extended-release amantadine, or adenosine A2A antagonists, has been demonstrated to reduce total OFF time, but patients still have OFF episodes. Taking an additional dose of levodopa for an acute episode is another common strategy, but is generally not helpful as it takes about 60 minutes for oral levodopa to take effect. The key to treating an OFF episode once it occurs is to use a medication that bypasses the dysfunctional gut. Three medications—inhaled levodopa, subcutaneous apomorphine injection, and sublingual apomorphine film—are approved for OFF episodes and avoid the dysfunctional GI system.

Inhaled levodopa uses a breath-actuated inhaler to deliver 84 mg of inhaled levodopa (equivalent to 50 mg orally) via the pulmonary system, thereby bypassing the GI system. In double-blind placebo-controlled studies, it began to work in as early as 10 minutes, provided significant relief at 30 minutes, and maintained its effect in the majority of patients at 60 minutes. The main adverse effect was cough and therefore this medicine should be avoided in patients with a history of lung disease.

Apomorphine is one of the oldest medications used for the treatment of PD. It is a short-acting D1- and D2-like receptor agonist and is the only drug proved to have an efficacy equal to that of levodopa. Both subcutaneous injections and sublingual strips avoid the GI system.
Subcutaneous apomorphine injection has been demonstrated to work in 4 to 12 minutes with a levodopa-like benefit lasting 40 to 90 minutes, reversing 95% of OFF episodes in study findings. Sublingual apomorphine film is absorbed systemically via the oral mucosa, avoiding first-pass metabolism. It has been demonstrated to work in as soon as 15 minutes, with significant improvement at 30 minutes, lasting up to 90 minutes. Approximately 80% of OFF episodes were aborted with sublingual film. The adverse effect profile of the different apomorphine products is similar; both are generally well tolerated, with nausea, vomiting, and somnolence being the most common adverse events. Injections were also associated with injection site reactions and the film was associated with oropharyngeal irritation. Both medications need to be titrated initially under medical supervision due to the potential for hypotension during titration.

Given the availability of safe and effective medications to treat OFF episodes on demand and the marked negative impact of such episodes on patients and caregivers, it is time to shift the paradigm in PD treatment. Just as neurologists and primary care physicians use both prophylactic and abortive therapies in migraine, it is time to use on-demand therapies in PD when OFF episodes occur despite adjunctive therapies and carbidopa levodopa. One challenge to shifting this paradigm is that all the on-demand therapies in PD are specialty pharmaceuticals and carbidopa levodopa. It is time to use both prophylactic and abortive therapies in migraine, it is time to use on-demand therapies in PD when OFF episodes occur despite adjunctive therapies and carbidopa levodopa. One challenge to shifting this paradigm is that all the on-demand therapies in PD are specialty pharmacy medications, and thus may be too expensive for some patients. Nevertheless, we should advocate for all our patients to have access to these important on-demand medications.

REFERENCES

FDA Advisory Committee Is Set to Reconvene on ALS Treatment
By Marco Meglio
The FDA's Peripheral and Central Nervous System Drugs Advisory Committee is planning to reconvene on September 7, 2022, to discuss the new drug application (NDA) for AMX0035 (Amylyx Pharmaceuticals), an investigational agent in review for amyotrophic lateral sclerosis (ALS), weeks before the scheduled Prescription Drug User Fee Act (PDUFA) date.1

The news comes less than a month after the agent received approval in Canada, making it the first new therapy for the disease since 2018.2 It also comes a few months after the original discussion by the committee. This second meeting of the panel will also feature a discussion on whether AMX0035 demonstrated significant enough efficacy in the phase 2 CENTAUR study (NCT03127514) and open-label extension, the basis of the NDA.

AMX0035, an orally administered fixed-dose coformulation of sodium phenylbutyrate-taurursodiol, originally had a PDUFA target action date of June 29, 2022, which was then pushed back to September 29, 2022, to allow the FDA more time to review data.3

For a full list of references, see the article on NeurologyLive.com.

READ MORE neurologylive.com/amx0035-advisory

FDA Accepts Alzheimer Disease Treatment Application
By Marco Meglio
The FDA has accepted and granted a priority review to Eisai and Biogen's biologics license application of lecanemab, an investigational agent to treat mild cognitive impairment due to Alzheimer disease (AD). The companies submitted the application in May 2022 and have been given a Prescription Drug User Fee Act action date of January 6, 2023.1

Submitted under the accelerated approval pathway, the application was supported by data from the phase 2b proof-of-concept clinical trial, Study 201 (NCT01767311). Additionally, the FDA will consider and review results from the ongoing phase 3 Clarity AD study (NCT03887455), which will serve as complementary data to verify the clinical benefit of lecanemab post approval. Depending on the results of Clarity AD, Eisai will submit an application for standard approval of lecanemab to the FDA before the end of the first quarter in 2023.

Lecanemab, an anti–amyloid beta (Aß) protofibril antibody, is designed to neutralize and eliminate soluble toxic Aß aggregates that are thought to contribute to the neurodegenerative process in AD. Study 201, a Bayesian design clinical trial, randomly assigned 856 patients with early AD with a confirmed presence of amyloid pathology to lecanemab at multiple doses (2.5 mg/kg biweekly, 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg monthly, and 10 mg/kg biweekly) or placebo. Investigators identified 10 mg/kg biweekly as the effective dose, which achieved at least 90% of the maximum treatment effect.

For a full list of references, see the article on NeurologyLive.com.

READ MORE neurologylive.com/lecanemab-application
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Multimedia highlights from our coverage of neurologic disorders

TOP TWEETS

Mayo Clinic Neuro | @MayoClinicNeuro
This week’s Neurology #ScholarlySaturday features: Dr Sean Pittcock and @ANASTASIA_ZEK talk to @marco-meglio1 and @neurology_live about pioneering care for autoimmune disorders through research and results. https://t.co/5cx0cX0d5T

Cure CMD | @CureCMD
Did you attend our SciFam Conference? Hear from our executive director Rachel & scientific director Gustavo on the benefits of attending courtesy of @neurology_live. https://neurologylive.com/view/cure-cmd-benefits-annual-scientific-family-conference

AASM Membership | @AASMmembership
At #SLEEP2022, AASM member Galit Dunietz, PhD, MPH, provided insight on women’s health, menopause cycles, and how sleep can have a direct impact on long-term cognitive health. Read more from @neurology_live: https://t.co/sPyTfEGeGR

Shepherd Center | @ShepherdCenter
Click the link to check out Louise’s interview with @neurology_live! @DrBackus https://t.co/zleBvvefW

UCSF Pediatric Brain Center | @UCSF_PBC
In this @neurology_live webinar segment, Joseph Sullivan, MD, and Kelly Knupp, MD, discuss the clinical signs and symptoms of Dravet Syndrome that go well beyond seizures and what they look for in young patients. https://t.co/bTnSlgoOo3

EXPLOITING ANTI-CD3 ANTIBODIES, RELEVANT BIOMARKERS IN PROGRESSIVE MS: TANUJA CHITNIS, MD
The associate neurologist at Brigham and Women’s Hospital provided insight on the current state of promising targets in progressive multiple sclerosis and why anti-CD3 therapy might be a new consideration for future trials. + VIEW VIDEO neurologylive.com/chitnis-anticd3

MENTAL HEALTH AND ADVOCACY IN PEDIATRIC MIGRAINE
Serena L. Orr, MD, MSc, a pediatric neurologist and headache specialist at the University of Calgary and Alberta Children’s Hospital, spoke about her recent work examining mental health conditions among pediatric patients with migraine, as well as how the field has progressed in managing the disease and advocating for these individuals. + LISTEN neurologylive.com/mm-ep-67

EXPANDING KNOWLEDGE ON ADVANTAGES OF LOW-SODIUM OXYBATES: RICHARD BOGAN, MD, FCCP, FAASM
The associate clinical professor at the University of South Carolina School of Medicine discussed how JZP-258’s clinical profile has expanded since its original approval for narcolepsy, and whether it makes sense for all patients to consider taking the drug. + VIEW VIDEO neurologylive.com/bogan-oxybates

MENTAL HEALTH AND ADVOCACY IN PEDIATRIC MIGRAINE
Serena L. Orr, MD, MSc, a pediatric neurologist and headache specialist at the University of Calgary and Alberta Children’s Hospital, spoke about her recent work examining mental health conditions among pediatric patients with migraine, as well as how the field has progressed in managing the disease and advocating for these individuals. + LISTEN neurologylive.com/mm-ep-67

UPDATES IN ESSENTIAL TREMOR CARE
Rajesh Pahwa, MD, a professor of neurology and director of the Parkinson’s Disease and Movement Disorder Center at The University of Kansas Medical Center, discussed the current state of treatment for essential tremor, including therapeutic and surgical options for this population. He shared his perspective on the latest advances in clinical care and diagnosis, the role of the patient-physician relationship, and the research into the disease’s underlying processes. + LISTEN neurologylive.com/mm-ep-68

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Plasma Neurofilament Level Is Correlated With Symbol Digit Modality Scores Following Ozanimod Treatment

By Marco Meglio

RESULTS FROM A POST HOC ANALYSIS of the SUNBEAM trial (NCT02294058) showed a negative association between plasma neurofilament light (pNfL) concentration and Symbol Digit Modalities Test (SDMT) score among patients with relapsing multiple sclerosis (MS). Patients treated with ozanimod (Zeposia; Bristol Myers Squibb) demonstrated decreased pNfL levels while improving SDMT scores to a greater extent than those receiving the comparator drug, interferon beta-1a.1

Senior author Jeffrey A. Cohen, MD, director of the Mellen Center for MS Treatment and Research at the Cleveland Clinic, presented the data at the 2022 Consortium of Multiple Sclerosis Centers Annual Meeting, June 1 to 4, in National Harbor, Maryland. The post hoc analysis specifically evaluated relationships between pNfL concentration, analyzed with Simoa technology, and SDMT scores, a secondary end point of the trial.

The study included 1346 patients (mean age, 35.6 years [± 9.3]) with relapsing MS who were treated with either oral ozanimod 0.92 mg (n = 447) or 0.46 mg (n = 451), or weekly intramuscular interferon beta-1a 30 µg (n = 448) for 12 months. Relationships between pNfL level and SDMT score at baseline were evaluated with Kendall tau correlation, and changes on treatment were assessed with linear regression and treatment-stratified bootstrap sampling.

At baseline, the median pNfL concentration was 14.7 µg (interquartile range [IQR], 10.2-23.3 pg/mL) and SDMT score was 48.0 (IQR, 38.0-56.0). The Kendall tau correlation between these variables was –0.10 (95% CI, –0.14 to –0.06), indicating a slightly negative association. Based on 1000 bootstrap samples, greater median percentage reduction in pNfL levels were associated with a greater mean SDMT score change from baseline to the end of the observation period.

Compared with those receiving interferon beta-1a, patients in both ozanimod dose groups had greater median reductions in pNfL and mean improvements in SDMT score, with the higher-dose group representing the greatest differences. Additionally, at the end of the 12-month treatment period, no relationships were found between baseline pNfL level or change from baseline in any of the specific SDMT scoring categories (worsened, stable, or improved defined as ≥ 4-point change).

Ozanimod, a sphingosine-1-phosphate receptor, was approved by the FDA for the treatment of adults with relapsing forms of MS in 2020, with data from SUNBEAM and RADIANCE part B (NCT01628393) as supportive evidence. In SUNBEAM, the annualized relapse rates were 0.35 (95% CI, 0.28-0.44) for interferon beta-1a compared with 0.18 (95% CI, 0.14-0.24) for the ozanimod 0.92-mg group and 0.24 (95% CI, 0.19-0.31) for the 0.46-mg group, for respective rate ratios of 0.52 (95% CI, 0.41-0.66; P < .001) and 0.69 (95% CI, 0.55-0.86; P = .001).2

In addition to reduced annualized relapse rate, treatment with ozanimod was associated with a 63% relative reduction of T1-weighted gadolinium-enhanced lesions, and a 48% relative reduction in new or enlarging T2 lesions at 1 year in SUNBEAM.3 Similar reductions also were observed at 2 years in RADIANCE.3 Notably, there was no significant difference in confirmed disability progression between the 2 study drugs at 3 and 6 months.

Recently, at the April 2022 American Academy of Neurology Annual Meeting, data from RADIANCE and its open-label extension DAYBREAK...
Women With MS Use Social Media to Discuss Safety Concerns on DMT Use in Pregnancy

By Matt Hoffman

PRELIMINARY RESULTS OF A STUDY of women with multiple sclerosis (MS) suggest that they engage with one another on social media platforms to discuss and share knowledge to better understand their treatment options during the family planning phase of their lives.

The group of investigators, led by Riley Bove, MD, an associate professor of neurology at UCSF Weill Institute for Neurosciences, used the social media listening platform Brandwatch to assess 2437 total mentions on Twitter, Tumblr, Reddit, forums, blogs, and YouTube for prespecified keywords and fetch English mentions of disease-modifying therapy (DMT) use in women with MS from August 18, 2020, to August 18, 2021. Each mention of keywords was categorized by its sentiment, defined as positive, neutral, or negative; these were validated and manually tagged to identify women who had been, were currently, or were planning to become pregnant or planning to breastfeed.

All told, investigators manually analyzed 585 unique mentions, of which 255 related to DMTs. Bove presented the findings at the 2022 Consortium of Multiple Sclerosis Centers Annual Meeting, June 1 to 4, in National Harbor, Maryland.

The major themes identified among the population—which included women planning pregnancy (n = 77) or currently pregnant or breastfeeding (n = 127)—were doubts about treatment or treatment delay due to safety concerns. Notably, though, DMTs were perceived as safe when they were recommended by health care providers (HCPs). Among women who had been pregnant (n = 34), most mentions related to eagerness for treatment in the postpartum period.

Bove et al wrote that it was unclear whether this social media engagement was occurring out of a desire for additional peer support or from a lack of sufficient discussion between women with MS and their physicians. “This study aims to raise awareness among HCPs around key concerns and educational gaps in women with MS and encourage proactive discussion around family planning as part of routine care,” they wrote.

When asked about the concerns about potential poor communication between physicians and patients, Bove told NeurologyLive®, “Most people posting reported pretty positive sentiments toward their clinicians. They weren’t going [on social media] because they were upset or distrustful. They were going there to augment and enrich their knowledge and the support they [had received].”

Bove also expressed her surprise at the positivity expressed by some individuals about certain medications during their pregnancy and lactation periods. Among the posts that mentioned known DMTs (n = 181), ocrelizumab (Ocrevus; Genentech) had the most mentions with 44, followed by glatiramer acetate (Copaxone; Teva Pharmaceuticals) with 41, and natalizumab (Tysabri; Biogen) with 29. Most mentions of ocrelizumab and glatiramer acetate were related to safety and were categorized by Bove et al as neutral to positive.

“For a long time, we’ve really abandoned these patients—we know that they’re at a very high relapse risk post partum. Not everybody, but about one-third of people, have relapses post partum and about half have new brain lesions, even in the absence of relapses,” Bove said.

“This is a population that is one of the most at risk, period, for relapse in the whole clinical course, and we’ve basically said, ‘Well, it’s unethical to treat you, so either you breastfeed or you start your meds,’ or ‘Stop your meds, even if you’re going to have a rebound.’ We always assume that the patients don’t want any drug exposure whatsoever, and in fact, what you see is that they’re quite nuanced. They interpret the risks and they learn that some medicines are safer than others. Seeing patients really grapple with that information, with the real-world data, and then convey that information to others, I think, was really positive.”

The investigators acknowledged that MS is often diagnosed in women of childbearing age but noted that “while multiple [DMTs] are available, most are not approved for women who are pregnant, trying to become pregnant, or breastfeeding. Where available, practice guidelines vary by region, and advice can differ between [HCPs].” As such, women with MS who are pregnant or lactating are often forced to weigh potential risks to their health and that of their offspring, as treatment discontinuation of DMTs can result in disease activity and progression.

This study is one of many in a growing group of literature to evaluate the effects of MS and treatment with DMTs in patients who are of childbearing age or pregnant. In July 2021, findings published in Neurology suggested that natalizumab might be an effective treatment option to minimize the risk of postpartum relapses in pregnant women with MS who pause DMT treatment during...
MAGNIMS Score Predicts Risk of Disability Deterioration Over Time

By Marco Meglio

RESULTS FROM A POST HOC ANALYSIS of the phase 3 OPTIMUM study (NCT02425644) show that the Magnetic Resonance Imaging in MS (MAGNIMS) score predicted long-term risk of disability worsening for patients with multiple sclerosis (MS) who had suboptimal response to treatment with either ponesimod (Ponvory; Janssen) or teriflunomide (Aubagio; Sanofi).\(^1\)

Participants with MS were randomly assigned 1:1 to either 20-mg ponesimod or 14-mg teriflunomide, the comparator drug, or placebo for 108 weeks. Patients were classified as 0, 1, or 2 on MAGNIMS score at week 60, with higher scores indicating worse clinical outcomes. The data were presented at the 2022 Consortium of Multiple Sclerosis Centers Annual Meeting, June 1 to 4, in National Harbor, Maryland.

Led by Alexander Keenan, MA, global market access leader at Johnson & Johnson, the investigators reported that significantly more patients taking ponesimod had a MAGNIMS score of 0 at week 60 (57% vs 46%; odds ratio [OR], 1.56; \(P < .001\)) and significantly fewer patients were classified as having a score of 2 (13% vs 20%; OR, 0.59; \(P = .002\)) relative to those on teriflunomide. To understand whether MAGNIMS scores at week 60 could differentiate the risk of times to 12- and 24-week confirmed disability accumulation (CDA) at week 108, the investigators used Cox regression analysis.

A total of 1061 patients were pooled from the 2 groups (ponesimod, \(n = 533\); teriflunomide, \(n = 528\)), with 51%, 32%, and 17%, of patients assigned MAGNIMS scores of 0, 1, and 2, respectively. At week 108, the risk of CDA significantly differed and was predictive of MAGNIMS scores from both the 12- and 24-week CDA. For the 12-week CDA, the HRs were 1.97 (\(P = .002\)) for 1 vs 0, and 3.48 (\(P < .001\)) for 2 vs 0, indicating that patients with a higher MAGNIMS score at week 60 had a higher risk of experiencing a 12-week CDA. For 24-week CDA, the HRs were similar: 1.99 (\(P = .007\)) for 1 vs 0, and 4.14 (\(P < .001\)) for 2 vs 0.

“Treatment with ponesimod resulted in more patients being classified with a favorable MAGNIMS score at week 60 than treatment with teriflunomide, but long-term effects on CDA need to be further confirmed in future research,” Keenan et al wrote.

Although this was the first analysis using MAGNIMS score to evaluate ponesimod and teriflunomide, the tool has been used in previous studies. One such 2021 study looked at the association of 1-year MAGNIMS score with long-term CDA in patients treated with interferon beta-1a.

In that study, patients received the medication 3 times weekly and were classified by MAGNIMS score (0, \(n = 129\); 1, \(n = 108\); 2, \(n = 130\), similar to OPTIMUM participants. The investigators found that the risk of CDA was higher at 1 year with a MAGNIMS score of 1 vs 0 (HR, 1.82; 95% CI, 1.38-2.41), 2 vs 0 (HR, 2.63; 95% CI, 2.01-3.45) and 2 vs 1 (HR, 1.45; 95% CI, 1.11-1.89), all of which were significant (\(P < .0001\)). The same outcome was observed with the risk of confirmed Expanded Disability Status Scale progression (1 vs 0: HR, 1.93 [95% CI, 1.23-3.02]; 2 vs 0: HR, 2.95 [95% CI, 1.95-4.46]; 2 vs 1: HR, 1.53 [95% CI, 1.05-2.23]; \(P < .0001\)).\(^2\)
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To nominate, please visit NeurologyLive.com/GiantsofMS/Nominate

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Highly Effective Gene Therapies for SMA: Where Do We Go From Here?

Neuromuscular medicine has entered an era of genetic therapy, opening the doors to questions about possible combination approaches and earlier initiation of treatment.

By Elizabeth A. Kichula, MD, PhD*; and John F. Brandsema, MD**

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SPINAL MUSCULAR ATROPHY (SMA) has traditionally been one of the most devastating diagnoses to give within a pediatric neurology clinic. The advent of genetically targeted therapies, as well as the rapid expansion of newborn screening in the United States, has dramatically altered the natural history of the disease. A consistent theme emerging from experience thus far in the targeted treatment age is the importance of early diagnosis and intervention, as a more modest response to treatment is seen in those with longer disease duration and more severe symptoms at time of treatment initiation. Ongoing efforts to understand optimal treatment type and timing necessarily include the concept of combination therapies, although there is a paucity of evidence at this time regarding whether such an approach is superior to monotherapy.

SMA is caused by autosomal recessive mutations in the SMN1 gene. Approximately 95% of cases are caused by biallelic deletion of SMN1, whereas the remaining cases have at least 1 allele with another type of mutation, most commonly a point mutation, causing SMN1 to be nonfunctional. SMN2 remains active in those with SMA but produces insufficient amounts of survival motor neuron (SMN) protein compared with those produced by SMN1 because of a point mutation in SMN2 that leads to aberrant splicing. Insufficient amounts of SMN protein result in progressive motor neuron death, causing the main symptoms of SMA with progressive weakness, in addition to the lower motor neuron signs of areflexia and fasciculations. In the more severe forms of SMA, bulbar and respiratory weakness also occurs. SMN has multiple roles in various tissues of the body, and the exact mechanism that causes disease is still being studied.1

SMA classically presents as a range of phenotypes, with type 1 being the most common, accounting for about two-thirds of all diagnoses. Untreated, babies never attain the ability to sit, and need respiratory support by the age of 2 years. Children with type 2 never attain the ability to walk without treatment, whereas those with type 3 typically lose the ability to walk, either later in childhood or into adulthood. SMN2 copy number does not absolutely determine type, but it is the most critical factor: More copies of SMN2 typically lead to milder forms of disease as the amount of functional SMN protein increases. In general, those with infantile onset have only 2 copies whereas those with onset in later childhood more commonly have 3 to 4 copies,1 although exceptions to this correlation do occur.
### Current Treatment Options

There are 3 treatment options that target the root cause of SMA by increasing the amount of SMN protein (TABLE). Nusinersen (Spinraza; Biogen) and risdiplam (Evrysdi; Genentech) work by altering the splicing of SMN2 to increase the amount of functional SMN protein. Nusinersen is an antisense oligonucleotide that is given intrathecally, initially as 4 loading doses over 2 months and then every 4 months as maintenance. Risdiplam is a small molecule that similarly modulates SMN2 translation to increase intact SMN; it is given as an oral solution daily. Both SMN2 modulators are currently approved for all individuals with SMA, regardless of age or type. Onasemnogene abeparvovec-xioi (Zolgensma; Novartis Gene Therapies) is an in vivo gene therapy. It is an AAV9 vector containing a plasmid with SMN DNA. The vector infects cells, with a tropism that includes motor neurons, leaving the plasmid to continuously produce SMN protein. SMA has been an ideal target for early experience with gene transfer as it is a disease of protein insufficiency, not absence, so there are fewer tolerability concerns regarding immunogenicity. Other advantages include the genetic homogeneity of the disease as well as the size of the SMN transgene, which is able to fit into the vector used. As motor neurons, the primary target cells, do not divide, the gene therapy should be long lasting, as current long-term follow-up from initial study patients suggests. Positive antibodies to AAV9 can at times preclude its use. The agent is currently approved in the United States as a one-time intravenous administration in children less than 2 years of age.

All treatments have shown profound benefits in infantile-onset SMA compared with the natural history of the disease. Further, additional data continue to be published for nusinersen and risdiplam, with emerging data about intrathecal delivery of gene transfer, showing some benefit in older individuals. Real-world data are important in understanding expectations of response to treatment in populations not studied in the original trials, including in adults with SMA. The improvements are not as dramatic; however, it is important to note that in a neurodegenerative disease, even stability is a benefit in comparison with the natural history of continued decline.

### Importance of Early Diagnosis

Current therapies can help to increase SMN protein levels, which may help to rescue sick motor neurons and prevent future loss of these critical cells. Stabilization allows for collateral sprouting and reinnervation of the muscle. As motor neurons do not divide, there are no treatments at present that can replace lost motor neurons. In study after study, including those looking at a presymptomatic dosing of nusinersen, risdiplam, and onasemnogene, findings have shown the largest benefits from early treatment, leading to the addition of SMA to the Department of Health and Human Services’ Recommended Uniform Screening Panel in 2018. States in the US have worked to quickly add it to their newborn screening (NBS), and 97% of live births have screened for SMA as of mid-2022. NBS for SMA is a genetic test. It looks for the common deletion of SMN1; as such, it will miss about 5% of cases that are because of nondeletion mutations. If there remains concern for SMA despite normal NBS, testing should include both deletion assay as well as SMN1 sequencing.

Identification of SMA via NBS allows treatment to be started very early on in life, within the first 1 to 2 months. Results from clinical studies have shown that although many patients with 3 SMN2 copies treated presymptomatically will hit most major motor developmental milestones within typical windows, many infants with only 2 copies of SMN2 may go on to have some delays. This is heralded by what is seen clinically, where sometimes subtle decline in examination and symptoms can be seen over a short, 1- to 2-week period while treatment is being implemented.

Some states immediately report SMN2 copy number, whereas in other states it is not part of their NBS process. Confirming SMN2 copy number is important as it informs the urgency of treatment. Current recommendations are to treat all individuals with 2 to 4 copies.

### Table: Approved Genetically Targeted Treatments for SMA

<table>
<thead>
<tr>
<th>Therapy</th>
<th>FDA approval</th>
<th>Strategy</th>
<th>Target</th>
<th>Indication</th>
<th>Administration</th>
<th>Mechanism of action</th>
<th>Adverse effects requiring monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nusinersen</td>
<td>December 2016</td>
<td>Splicing modification</td>
<td>SMN2</td>
<td>Pediatric and adult patients</td>
<td>One time IV administration</td>
<td>Splicing modification of SMN2, primarily in CNS</td>
<td>• Coagulation and renal testing • Post–lumbar puncture syndrome</td>
</tr>
<tr>
<td>Onasemnogene abeparvovec-xioi</td>
<td>May 2019</td>
<td>Gene replacement</td>
<td>SMN2</td>
<td>Pediatric patients less than 2 years of age</td>
<td>Daily oral solution</td>
<td>Delivers SMN transgene that self-expresses SMN protein</td>
<td>• Hepatic inflammation • Vomiting • Thrombocytopenia • Elevated troponin • Thrombotic microangiopathy</td>
</tr>
<tr>
<td>Risdiplam</td>
<td>August 2020</td>
<td>Splicing modification (small molecule)</td>
<td>SMN2</td>
<td>Pediatric and adult patients</td>
<td>One time IV administration</td>
<td>Delivers SMN transgene that self-expresses SMN protein</td>
<td>• Potential effects on male fertility • Teratogenicity • GI issues/rash</td>
</tr>
</tbody>
</table>

CNS, central nervous system; GI, gastrointestinal; IV, intravenous.
of SMN2. Those with only 2 copies, or who have some signs of SMA on examination such as hypotonia, decreased reflexes, or subtle weakness, especially need to be urgently treated. Reflecting the “time is brain” mantra from the stroke literature, “time is motor neuron” in these cases. It is imperative that those who receive a diagnosis of SMA be seen quickly at sites that are familiar with the current treatments and are able to initiate treatment in a timely manner.

The importance of early treatment suggests a potential benefit to prenatal diagnosis via parental carrier testing, even in states with NBS. A prenatal diagnosis can include SMN2 copy number and allow the family more time to consider all treatments. Although the diagnosis is always inherently stressful, the result of positive NBS results in the immediate postnatal period, and the need to quickly decide on a treatment, can introduce additional stresses for the family. A prenatal diagnosis facilitates planning for pretreatment labs and genetic confirmation to be sent on the day of delivery, which may speed up this critical information by up to 2 to 3 weeks, further decreasing the time to treatment initiation. A prenatal diagnosis may also help to optimize the time of delivery, with consideration to induction at early term (ie, 38 or 39 weeks), although obstetric factors must also be carefully considered.

The potential to treat in utero is intriguing. Children can be symptomatic at birth, sometimes so significantly that infant cases are sometimes called SMA type 0, and more often with subtle findings of abnormal electrophysiology such as reduced compound muscle action potential amplitude or abnormal fasciculations on muscle ultrasound commonly seen at the first visit. There are currently no treatments that are available in utero. Gene therapy, as a one-time injection to the fetus, could be an option, but the safety of such administration remains unclear. Risdiplam can cross the placental barrier if administered to the mother; however, teratogenicity was identified preclinically and so risks/benefits and optimal timing of treatment in such situations again remain unclear.

Combination Therapy
One very active area of debate within the SMA community is the potential benefit (or lack thereof) of combination treatment. Most combination treatment at this time considers the combination of gene transfer with an SMN2 splice modifier. Onasemnogene does not result in the transduction of 100% of motor neurons in animal models, and so the additional SMN2 modulator may have some additional benefit. There are some data supporting the overall safety of gene transfer with risdiplam and/or nusinersen. Findings from some studies have suggested increased adverse effects from onasemnogene in patients who previously received nusinersen; however, those also tended to be older individuals and it is unclear whether age and/or nusinersen exposure may be more critical. Risdiplam may also have more systemic effects relative to the targeting of the central nervous system with intrathecal nusinersen delivery. It is very challenging to show whether there is additional benefit of a combination approach given the heterogeneity among the experience of individuals with SMA and what has been seen thus far in terms of variability in response to monotherapy. Even children who are treated with monotherapy commonly go through periods of relative plateau before having significant gains again. The RESPOND trial (NCT04488133) is an ongoing open-label study of infants and young children receiving nusinersen after gene transfer. The JEWELFISH study (NCT03032172) is an ongoing study of patients receiving risdiplam after a prior SMA treatment, a subgroup of whom received gene transfer before risdiplam initiation. The data from these trials will augment early real-world experience with combination therapy.

Many individuals with SMA started on nusinersen after approval in late 2016 and then may have switched over to risdiplam once it became available in mid-2020 in the United States, and in some cases “switched back” to nusinersen as well. This is not true combination therapy as generally it is more of a transition between therapies. The ASCEND study (NCT02594124) of nusinersen did receive combination treatment with commercial risdiplam after its approval. The majority of American health care plans limit patients to only 1 of these medications at this time.

Optimal timing of treatment(s) initiation may not be the same for every individual with SMA. Potential for toxicities with high levels of SMN expression, as recently described in mouse models, is another factor to consider. When 2 therapies are given close together, the potential interactions and adverse effects may be harder to separate. However, there is reason to think that earlier on in the disease may be the most effective time for combination treatment, particularly in symptomatic infants who would be predicted to manifest SMA type 1 or type 2 without treatment.

SMN-Independent Treatments
More recent trials have focused on alternative medications and treatments that may work in tandem with SMN replacement therapies, as well as in isolation, to further improve muscle strength. The most advanced of these is myostatin inhibitors, with several active clinical trial programs and promising early data presented in 2022. It remains to be seen whether these may have additional effects in those who are currently in a more chronic state of disease, who do not receive the same benefit from SMN targeted therapies as those who are newly symptomatic or presymptomatic.

Optimizing standard of care in patients with SMA who have been treated with targeted therapies requires an understanding of the new phenotypes seen in these populations. Interdisciplinary team management allows for maximizing functional outcomes. The impact of development in those treated early, and further changes with puberty and senescence over the life span, will be further clarified with experience. Short- and long-term toxicities of various treatment approaches will be identified via careful follow-up. A genetic diagnosis of SMA has different implications in this age of treatment, but those affected will continue to require a lifelong relationship with an SMA-focused care team to ensure the best outcomes.
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Migraine is a Highly Prevalent and debilitating disorder characterized by a unilateral hemicranial pulsating headache with accompanying symptoms (ie, sensory disturbances and nausea). Migraines occur most often in persons aged 20 to 50 years and are more common in women. Migraines are currently treated with acute and preventive therapies; however, because the pathophysiology of migraine is still largely elusive, treatment response remains difficult to predict. Migraine pain is widely recognized to be caused by a lowered threshold of nociceptive signaling in response to proinflammatory agents, and environmental and hormonal triggers have been linked to migraine initiation. Prolonged activation of the trigeminovascular system can, in turn, lead to persistent nociceptive signaling, which creates a positive feedback loop whereby the persistent release of neuropeptides from sensory neurons increases pain impulses that are transmitted to the nucleus trigeminalis caudalis. This clinical endocannabinoid (eCB) deficiency is also common in other major functional pain disorders.

Current standards of care for migraine include β-blockers, antiepileptic drugs, triptans, and analgesics, which exhibit moderate effectiveness, limited tolerability, and may induce weight gain, depression, chest pain, and gastrointestinal and cardio-renal effects. Investigational migraine treatment aims to abort attacks or to reduce attack frequency, duration, and intensity; however, only a minority of patients actually achieve these outcomes in clinical trials. Potential novel targets for antimigraine drugs include those that reduce central sensitization and suppress cortical spreading depression (CSD).

The eCB system (ECS) is a comprehensive signaling system present in nearly every cell type that functions to reduce pain and alleviate neurodegenerative and inflammatory damage. The ECS regulates pain signals by inhibiting the release of neurotransmitters controlling nociceptive inputs and the levels of inputs known to be involved in transmission and modulation of pain signals. The ECS consists of endogenous phospholipid-based ligands, their molecular targets (G protein–coupled cannabinoid receptors: type 1 [CB1] and type 2 cannabinoid receptors [CB2]), protein transporters, and synthetic and degradation enzymes (FIGURE). Whereas CB1 is expressed abundantly in the brain, CB2 is primarily expressed in peripheral tissues. CB1 and CB2 receptors also form heteroreceptor complexes in microglia, which are activated by CSD and thus may contribute to the pathogenesis of migraine with aura. Indeed, CB1 receptor gene variants increase the risk of migraine with aura. Targeting CB1 receptors is an attractive strategy for migraine treatment, promising block peripheral and central nociceptive traffic to reduce pathologically enhanced cortical excitability.

The best-characterized ECS signaling molecules are the eCBs arachidonoyl ethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), which typically act to amplify or dampen the perception of pain. N-acylphosphatidylethanolamine-phospholipase D and sn-1-specific diacylglycerol lipase synthesize AEA and 2-AG, respectively, from precursors in the phospholipid membrane. These eCBs are synthesized on demand and are not stored. After binding to the CB1 and CB2 receptors, cannabinoids are enzymatically degraded and removed from the body. Disturbances in the supply or functionality of eCB ligands have been connected to mental state disturbances, including migraine, suggesting a correlation between deficient levels of eCBs and pain. Indeed, aberrant catabolic pathways have been identified in patients with migraine. In fact, evidence suggests that lower levels of AEA and 2-AG in women may correspond with increased incidence of migraines.

Additional targets for eCBs include the CB3 receptor GPR55, peroxisome proliferator-activated receptors alpha and gamma, and the transient receptor potential vanilloid 1 (TRPV1) ion channel. Cannabinoid and TRPV1 receptors are often found in the same organs, tissues, and cells, where they can have opposing or similar functions in pain and inflammation. Whereas 2-AG is a full agonist for CB1 and CB2, AEA is largely selective for the CB1 receptor, though it also binds to TRPV1, suggesting an alternative strategy for managing migraine.
April from eCBs, other sources of cannabinoids include the phytocannabinoids (pCBs) produced by plants of the genus Cannabis and synthetic cannabinoids that can interact with cannabinoid receptors. Both CB1 and CB2 respond to endogenous ECS signals from eCBs, as well as signals from pCBs, which are propagated by exogenous cannabinoids, most notably tetrahydrocannabinol (THC).

Cannabis exhibits analgesic, immunomodulatory, and anti-inflammatory effects. Only a few cannabinoid drugs have been rigorously tested for safety and efficacy and have been approved for use at the national level: dronabinol (Marinol) for anorexia and weight loss and for chemotherapy-induced nausea and vomiting (CINV); nabilone (Cesamet) for CINV; rimonabant (Acomplia) for weight management, dyslipidemia, and type II diabetes; nabiximols (Sativex) for spasticity; and cannabidiol (Epidiolex) for seizures. A growing number of US states and other nations have legalized the use of Cannabis sativa for medicinal purposes, although evidence-based data regarding its clinical utility remain incomplete.

A major concern about this therapeutic approach is that long-term use of cannabis can cause a physical reliance on pCBs (eg, THC) and drug tolerance, which may result in reduction or loss of experienced pain relief. Moreover, headache itself is an adverse effect (AE) associated with cannabinoid medications and is common with cannabis withdrawal. Indeed, cannabinoid overuse in rodent models induced latent sensitization, which increased their sensitivity to stress, suggesting that vulnerable individuals using cannabinoids may have increased risk of developing medication overuse headache. Nonetheless, short-term exposure to eCBs is capable of evoking plastic changes to brain regions that regulate pain sensation. Preclinical and clinical findings suggest a possible role for eCBs and related lipids, such as palmitoylethanolamide (PEA), in migraine-related pain treatment. A multicenter, double-blind, placebo-controlled study (NCT00123201) of the safety and efficacy of dronabinol, which was delivered with a metered dose inhaler for the treatment of migraine, was completed in 2015 but no results have been published.

Alternative strategies for leveraging cannabinoid drugs in migraine management include using low-dose, selective, or alternative ligands and/or targeting alternative pain-implicated pathways, all of which can overcome the psychotropic AEs of CB1 receptor activation. Lowered inhibitory activity of eCBs in migraine, possibly due to reduced CB1 and CB2 receptor expression, supports the contention that compensatory therapy with exogenous cannabinoids at low doses is enough. Low-dose cannabinoids combined with nonsteroidal anti-inflammatory drugs (NSAIDs) could result in analgesia without the AEs associated with large doses of either cannabinoids or NSAIDs alone. Aside from modulating CB1 receptors, targeting CB2 receptors in immune cells can also reduce inflammation. Other endogenously produced molecules (eg, oleamide, O-arachidonoyl ethanolamine, 2-AG ether, and N-arachidonoyl-dopamine) influence the function of CB receptors. eCB-like mediators (eg, N-acyl-taurines, N-acyl-serotonins, N-acyl-dopamines, fatty acid primary amides, and N-acyl-amino acids) have heterogeneous targets, such that they can affect biological processes in the central nervous system without acting primarily through CB1/CB2 receptors. The pCB cannabidiol, unlike THC, also acts on non–CB1/CB2 receptors such as TRPV1 to reduce inflammation and neuropathic pain without concerns about intoxication and psychoactive effects.

Structural analogues of eCBs (ie, N-oleylethanolamine and PEA) exhibit low affinity for cannabinoid receptors, instead serving as alternative substrates for catalytic enzymes and thus increasing the potency of eCBs. Preliminary evidence suggests that inhibiting enzymes that break down 2-AG is also effective for reducing headache-like pain. Overall, cannabinoid-based migraine treatment should be a successful contender as a new migraine therapy, as cannabinoid treatment may overcome the AEs of existing antimigraine drugs, provide a more inclusive and effective mode of therapy, and provide anticonvulsive, analgesic, antiemetic, and anti-inflammatory effects to combat migraine-associated pain.

Ultimately, the successful development of compounds that modulate the ECS for pain relief in humans will depend on the ability to separate psychotropic effects from therapeutic ones and to limit potential off-target interactions. The ECS may be dysfunctional in migraine and may interact with numerous parallel pathways. As such, additional studies are required to explore the neurobiological mechanisms and neural circuits of the ECS that are implicated in migraine.

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For a full list of references, see the article on NeurologyLive.com.

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INDICATION
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Contraindications:
- Patients who in the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure or have a presence of Mobitz type II second-degree or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker
- Patients with severe untreated sleep apnea
- Patients taking a monoamine oxidase (MAO) inhibitor

Infections: ZEPOSIA may increase the susceptibility to infections. Life-threatening and rare fatal infections have occurred in patients receiving ZEPOSIA. Obtain a recent (i.e., within 6 months or after discontinuation of prior MS therapy) complete blood count (CBC) including lymphocyte count before initiation of ZEPOSIA. Delay initiation of ZEPOSIA in patients with an active infection until the infection is resolved. Consider interruption of treatment with ZEPOSIA if a patient develops a serious infection. Continue monitoring for infections up to 3 months after discontinuing ZEPOSIA.
- Herpes zoster was reported as an adverse reaction in ZEPOSIA-treated patients. Herpes simplex encephalitis and varicella zoster meningitis have been reported with sphingosine 1-phosphate (SIP) receptor modulators. Patients without a healthcare professional-confirmed history of varicella (chickenpox), without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating ZEPOSIA. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ZEPOSIA.
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WITH ZEPOSIA, YOU HAVE THE POWER TO HELP PRESERVE THEIR MOST VALUABLE RESOURCE

- **Powerful efficacy** in reducing ARR, GdE lesions, and new/enlarging T2 lesions vs Avonex\(^a\) and generally similar safety demonstrated in the long-term extension study\(^d\)
- **Data on brain volume and cognitive processing speed (SDMT)** in secondary, exploratory endpoints and post hoc analysis\(^b\)
- **Safety comparable to Avonex in overall incidence of adverse reactions\(^e\) and generally similar safety demonstrated in the long-term extension study\(^d\)**

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\(^a\)**Study designs:** SUNBEAM (1 year; N=1346) and RADIANCE (2 years; N=1313) were multicenter, randomized, double-blind, double-dummy, active treatment-controlled studies of daily oral ozanimod 0.46 mg (not approved for maintenance dose) or 0.92 mg vs weekly Avonex (interferon beta-1a), 30-μg intramuscular injection. **Primary endpoint:** ZEPOSIA reduced ARR vs Avonex by 48% at 1 year (0.181 vs 0.350, respectively) and by 38% at 2 years (0.172 vs 0.276, respectively). **Secondary endpoints:** ZEPOSIA reduced the number of new or enlarging T2 lesions by 48% at 1 year and by 42% at 2 years and reduced the number of GdE lesions vs Avonex by 63% at 1 year and 53% at 2 years. 9 of 10 patients showed no confirmed 3-month disability progression. There was no significant difference in 3-month confirmed disability between ZEPOSIA and Avonex.\(^c\)

\(^b\)**Brain volume loss** was analyzed as secondary (whole brain volume loss) and exploratory endpoints (thalamic volume loss and cortical grey matter volume loss) in the SUNBEAM and RADIANCE trials. **Volume loss endpoints were not part of the statistical analysis hierarchy.** SDMT is a tool that measures cognitive processing speed and was analyzed in a post hoc analysis of SUNBEAM and DAYBREAK, an ongoing open-label extension study. The MSFC was a secondary endpoint made up of 3 components: 9-hole peg test (arm/hand function), timed 25-foot walk (ambulation), and SDMT (cognitive function). SUNBEAM SDMT post hoc ZEPOSIA (n=427) Avonex (n=426) at Month 12. **DAYBREAK SDMT post hoc (SUNBEAM participants only): ZEPOSIA (n=376) at Month 42. SDMT was not part of the statistical analysis hierarchy for SUNBEAM and was analyzed descriptively in DAYBREAK.**

\(^c\)**Adverse reactions:** Overall incidence of adverse reactions for ZEPOSIA vs Avonex at 1 year was 59.8% and 75.5%, respectively, and at 2 years was 74.7% and 83.0%, respectively. Across 2 head-to-head trials, the most common adverse reactions with an incidence of at least 2% in patients treated with ZEPOSIA and at least 1% greater than Avonex, respectively, were as follows: upper respiratory infection, 26% (vs 22%); hepatic transaminase elevation, 10% (vs 9%); orthostatic hypotension, 4% (vs 3%); urinary tract infection, 4% (vs 3%); back pain, 4% (vs 3%); hypertension, 4% (vs 2%); and abdominal pain upper, 2% (vs 1%). Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control. Upper respiratory infection includes nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, mumps; respiratory tract infection viral, upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis. Hepatic transaminase elevation includes alanine aminotransferase increased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminase increased. Hypertension includes hypertension, essential hypertension, and orthostatic hypertension. **Severe adverse reactions:** The rate of severe adverse reactions at 1 year for ZEPOSIA was 1.6% vs 2.2% for Avonex and the rate at 2 years for ZEPOSIA was 3.5% vs 4.3% for Avonex. **Serious adverse reactions:** The rate of serious adverse reactions at 1 year for ZEPOSIA was 2.9% vs 2.5% for Avonex and the rate at 2 years for ZEPOSIA was 6.8% vs 6.4% for Avonex. Please see full Prescribing Information for additional SUNBEAM and RADIANCE data.

\(^d\)**Study design:** DAYBREAK is an ongoing open-label extension (OLE) trial that enrolled participants from multiple randomized phase 1 to 3 studies, including SUNBEAM and RADIANCE. These data are presented as an interim analysis with a data cutoff of February 2, 2021. Patients evaluated in this analysis included those receiving ZEPOSIA 0.92 mg (n=681) who completed the randomized phase 1 to 3 trials. **Primary objective** evaluated the long-term safety of ZEPOSIA. Secondary objectives included ARR, new/enlarging T2 lesions, and GdE lesions. Endpoints were analyzed descriptively.

**Treatment-emergent adverse events (TEAEs):** At the data cutoff (up to 5 years), the overall incidence of TEAEs for ZEPOSIA in the DAYBREAK OLE trial was 84.7%. The most common TEAEs with an incidence of at least 4% in patients treated with ZEPOSIA, sorted by decreasing incidence, were as follows: nasopharyngitis, 19.3%; headache, 15.6%; upper respiratory tract infection, 10.9%; ALC decreased, 8.9%; lymphopenia, 8.7%; back pain, 8.3%; gamma-glutamyl transferase increased, 5.9%; bronchitis, 5.8%; urinary tract infection, 5.8%; hypertension, 5.4%; respiratory tract infection, 5.4%; viral respiratory tract infection, 5.0%; and depression-related TEAEs, 4.9%. The rate of TEAEs leading to permanent treatment discontinuation was 2.7%. **Severe TEAEs:** The rate of severe TEAEs was 6.0%.

**Serious TEAEs:** The rate of serious TEAEs was 11.7%. ALC=absolute lymphocyte count; ARR=annualized relapse rate; GdE=gadolinium enhancing; MSFC=Multiple Sclerosis Functional Composite; RMS=relapsing multiple sclerosis; SDMT=Symbol Digit Modalities Test.

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information.
IMPORTANT SAFETY INFORMATION (CONTINUED)

Infections: (Continued)

- Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another S1P receptor modulator. If CM is suspected, ZEPOSIA should be discontinued until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.
- In clinical studies, patients who received ZEPOSIA were not to receive concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for treatment of MS. Concomitant use of ZEPOSIA with any of these therapies would be expected to increase the risk of immunosuppression. When switching to ZEPOSIA from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects.
- Use of live attenuated vaccines should be avoided during and for 3 months after treatment with ZEPOSIA. If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA.

Progressive Multifocal Leukoencephalopathy (PML): PML is an opportunistic viral infection of the brain that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability. PML has been reported in patients treated with S1P receptor modulators, including ZEPOSIA, and other MS therapies and has been associated with some risk factors. If PML is suspected, withhold ZEPOSIA and perform an appropriate diagnostic evaluation.

If confirmed, treatment with ZEPOSIA should be discontinued.

Bradyarrhythmia and Atrioventricular Conduction Delays: Since initiation of ZEPOSIA may result in a transient decrease in heart rate and atrioventricular conduction delays, dose titration is recommended to help reduce cardiac effects. Initiation of ZEPOSIA without dose escalation may result in greater decreases in heart rate. If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought for those individuals:

- with significant QT prolongation
- with arrhythmias requiring treatment with Class Ia or III anti-arrhythmic drugs
- with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension
- with a history of Mobitz type II second-degree or higher AV block, sick sinus syndrome, or sino-atrial heart block

Liver Injury: Elevations of aminotransferases may occur in patients receiving ZEPOSIA. Obtain liver function tests, if not recently available (i.e., within 6 months), before initiation of ZEPOSIA. Patients who develop symptoms suggestive of hepatic dysfunction should have hepatic enzymes checked and ZEPOSIA should be discontinued if significant liver injury is confirmed. Caution should be exercised when using ZEPOSIA in patients with history of significant liver disease.

Fetal Risk: There are no adequate and well-controlled studies in pregnant women. Based on animal studies, ZEPOSIA may cause fetal harm. Women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for 3 months after stopping ZEPOSIA.

Increased Blood Pressure: Increase in systolic blood pressure was observed after about 3 months of treatment and persisted throughout treatment. Blood pressure should be monitored during treatment and managed appropriately. Certain foods that may contain very high amounts of tyramine could cause severe hypertension in patients taking ZEPOSIA. Patients should be advised to avoid foods containing a very large amount of tyramine while taking ZEPOSIA.

Respiratory Effects: ZEPOSIA may cause a decline in pulmonary function. Spirometric evaluation of respiratory function should be performed during therapy, if clinically indicated.

Macular Edema: S1P modulators have been associated with an increased risk of macular edema. Patients with a history of uveitis or diabetes mellitus are at increased risk. Patients with a history of these conditions should have an ophtalmic evaluation of the fundus, including the macula, prior to treatment initiation and regular follow-up examinations. An ophtalmic evaluation is recommended in all patients at any time if there is a change in vision. Continued use of ZEPOSIA in patients with macular edema has not been evaluated; potential benefits and risks for the individual patient should be considered if deciding whether ZEPOSIA should be discontinued.

Posterior Reversible Encephalopathy Syndrome (PRES): Rare cases of PRES have been reported in patients receiving a S1P receptor modulator. If a ZEPOSIA-treated patient develops unexplained neurological or psychiatric symptoms or any symptoms suggestive of an increase in intracranial pressure, a complete physical and neurological examination should be conducted. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, treatment with ZEPOSIA should be discontinued.

Unintended Additive Immunosuppressive Effects From Prior Immunosuppressive or Immune-Modulating Drugs: When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects while at the same time minimizing risk of disease reactivation. Initiating treatment with ZEPOSIA after treatment with alentuzumab is not recommended.

Severe Increase in Multiple Sclerosis (MS) Disability After Stopping ZEPOSIA: In MS, severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of a S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping ZEPOSIA treatment so patients should be monitored upon discontinuation.

Immune System Effects After Stopping ZEPOSIA: After discontinuing ZEPOSIA, the median time for lymphocyte counts to return to the normal range was 30 days with approximately 90% of patients in the normal range within 3 months. Use of immunosuppressants within this period may lead to an additive effect on the immune system, therefore caution should be applied when initiating other drugs 4 weeks after the last dose of ZEPOSIA.

Most Common Adverse Reactions (≥ 4%): upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.

Use in Specific Populations: Hepatic Impairment: Use is not recommended.

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information.

ZEPOSIA® (ozanimod) capsules, for oral use

**INDICATIONS AND USAGE**

ZEPOSIA (ozanimod) is indicated for the treatment of:
- relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

**DOSAGE AND ADMINISTRATION**

**Assessments Prior to First Dose of ZEPOSIA**

Before initiation of treatment with ZEPOSIA, assess the following:

- Complete Blood Count
  - Obtain a recent (i.e., within the last 6 months or after discontinuation of prior MS therapy) complete blood count (CBC), including lymphocyte count (see Warnings and Precautions).

Cardiac Evaluation

Obtain an electrocardiogram (ECG) to determine whether preexisting conduction abnormalities are present. In patients with arrhythmias, including conditions, advice from a cardiologist should be sought (see Warnings and Precautions).

Liver Function Tests

Obtain recent (i.e., within the last 6 months) transaminase and bilirubin levels (see Warnings and Precautions).

**Ophthalmic Assessment**

In patients with a history of uveitis or macular edema, obtain an evaluation of the fundus, including the macula (see Warnings and Precautions).

**Current or Prior Medications**

- If patients are taking anti-neoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies, or [see Warnings and Precautions].

**ADVERSE REACTIONS**

**Obtain a recent (i.e., within the last 6 months) complete blood count (CBC), including lymphocyte count (see Warnings and Precautions).**

**Cardiac Evaluation**

Obtain an electrocardiogram (ECG) to determine whether preexisting conduction abnormalities are present. In patients with arrhythmias, advice from a cardiologist should be sought (see Warnings and Precautions).

**Liver Function Tests**

Obtain recent (i.e., within the last 6 months) transaminase and bilirubin levels (see Warnings and Precautions).

**Ophthalmic Assessment**

In patients with a history of uveitis or macular edema, obtain an evaluation of the fundus, including the macula (see Warnings and Precautions).

**Current or Prior Medications**

- If patients are taking anti-neoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies, or [see Warnings and Precautions].

**Ophthalmic Assessment**

In patients with a history of uveitis or macular edema, obtain an evaluation of the fundus, including the macula (see Warnings and Precautions).

**Current or Prior Medications**

- If patients are taking anti-neoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies, or [see Warnings and Precautions].
Increased Blood Pressure

In MS Study 1 and Study 2, patients treated with ZEPOSIA had an average increase of approximately 1 to 2 mm Hg in systolic pressure over patients who received IFN beta-1a, and no effect on diastolic pressure. The increase in systolic pressure was first detected after approximately 3 months of treatment and persisted throughout treatment. Hypertension was reported as an adverse reaction in 3.9% of patients treated with ZEPOSIA 0.92 mg and in 2.1% of patients who received IFN beta-1a. Two patients treated with ZEPOSIA in MS Study 1 and one patient treated with interferon (IFN) beta-1a in Study 2 experienced a hypertensive crisis that was not clearly influenced by a concomitant medication.

Blood pressure should be monitored during treatment with ZEPOSIA and managed appropriately.

Certain foods that may contain very high amounts (i.e., more than 50 mg) of tyramine could cause severe hypertension because of potential tyramine interaction in patients taking ZEPOSIA, even if the recommended doses. Because of an increased sensitivity to tyramine, patients should be advised to avoid foods containing a very large amount of tyramine while taking ZEPOSIA.

Respiratory Effects

Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV1) were observed in MS patients treated with ZEPOSIA as early as 3 months after treatment initiation. In the MS pooled analyses of Study 1 and Study 2, the decline in absolute FEV1 from baseline in patients treated with ZEPOSIA compared to patients who received IFN beta-1a was 60 mL (95% CI: -100, -20) at 12 months. The mean difference in percent predicted FEV1 at 12 months was 1.4%, 95% CI: (-2.6, -0.2), though significant reductions were not seen at other timepoints. There is insufficient information to determine the reversibility of the decrease in FEV1 or FVC after drug discontinuation. One patient in MS Study 1 discontinued ZEPOSIA because of dyspnea.

Spirometric evaluation of respiratory function should be performed during treatment with ZEPOSIA, if clinically indicated.

Macular Edema

Sphingosine 1-phosphate (S1P) receptor modulators, including ZEPOSIA, have been associated with an increased risk of macular edema.

In MS Study 1 and Study 2, macular edema was observed in 0.3% of patients treated with ZEPOSIA and in 0.3% of patients who received IFN beta-1a.

An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients at any time if there is any change in vision while taking ZEPOSIA.

Continuation of ZEPOSIA therapy in patients with macular edema has not been evaluated. A decision on whether or not ZEPOSIA should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Macular Edema in Patients with a History of Uveitis or Diabetes Mellitus

Patients with a history of uveitis and patients with a history of diabetes mellitus are at increased risk of macular edema during ZEPOSIA therapy. The incidence of macular edema is also increased in patients with a history of uveitis. In addition to the examination of the fundus, including the macula, prior to treatment, patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

Posterior Reversible Encephalopathy Syndrome

Rarer cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a S1P receptor modulator. In MS controlled clinical trials with ZEPOSIA, one case of PRES was reported. Should a ZEPOSIA-treated patient develop any unexpected neurological or psychiatric symptoms (e.g., cognitive deficits, behavioral changes, cortical visual disturbances, or any other neurological or cortical symptoms/signs), any symptoms suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination and should consider an MRI. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, treatment with ZEPOSIA should be discontinued.

Unintended Additive Immun suppressive Effects from Prior Treatment with Immunosuppressive or Immune-Modulating Drugs

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects while at the same time minimizing risk of disease reactivation, when initiating ZEPOSIA.

Initiating treatment with ZEPOSIA after treatment with alentuzumab is not recommended [see Drug Interactions].

Severe Increase in Multiple Sclerosis Disability after Stopping ZEPOSIA

In MS, severe exacerbation of disease, including disease reburden, has been rarely reported after discontinuation of a S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping ZEPOSIA treatment. Patients should be observed for a severe increase in disability upon ZEPOSIA discontinuation and appropriate treatment should be instituted, as required.

Immun System Effects after Stopping ZEPOSIA

After discontinuing ZEPOSIA, the median time for peripheral blood lymphocytes to return to the normal range was approximately 30 days with 85% to 90% of patients in the normal range within 3 months [see Clinical Pharmacology (12.2) in full Prescribing Information]. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore caution should be applied when initiating other drugs 4 weeks after the last dose of ZEPOSIA [see Drug Interactions].

ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

• Infections [see Warnings and Precautions]
• Bradycardia and Atrioventricular Conduction Delays [see Warnings and Precautions]
• Liver Injury [see Warnings and Precautions]
• Fetal Risk [see Warnings and Precautions]
• Increased Blood Pressure [see Warnings and Precautions]
• Respiratory Effects [see Warnings and Precautions]
• Macular Edema [see Warnings and Precautions]
• Posterior Reversible Encephalopathy Syndrome [see Warnings and Precautions]
• Unintended Additive Immun suppressive Effects from Prior Treatment with Immunosuppressive or Immune-Modulating Drugs [see Warnings and Precautions]
• Severe Increase in Multiple Sclerosis Disability after Stopping ZEPOSIA [see Warnings and Precautions]
• Immune System Effects after Stopping ZEPOSIA [see Warnings and Precautions]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Common Adverse Reactions

Multiple Sclerosis

The safety of ZEPOSIA was evaluated in two randomized, double-blind, active comparator-controlled clinical studies in which 882 patients received ZEPOSIA 0.92 mg [see Clinical Studies (14.1) in full Prescribing Information].

Table 2 lists adverse reactions that occurred in at least 2% of ZEPOSIA-treated patients and greater than comparator. The most common adverse reactions that occurred in at least 4% of ZEPOSIA-treated patients and greater than in patients who received IFN beta-1a were upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.

Table 2: Adverse Reactions with an Incidence of at Least 2% in ZEPOSIA (ozanimod)-Treated Patients and at Least 1% Greater than IFN beta-1a in Patients with Multiple Sclerosis (Pooled MS Study 1 and Study 2) (Continued)
There are no adequate data on the developmental risk associated with the use of ZEPOSIA in pregnant women.

**Risk Summary**

**Pregnancy**

Table 3: Clinically Relevant Interactions Affecting Drugs, Tyramine, and Vaccines Co-administered with ZEPOSIA (ozanimod)

<table>
<thead>
<tr>
<th>Prevention/Management</th>
<th>Clinical Impact</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-administration of ZEPOSIA with drugs or over-the-counter medications that can increase norepinephrine or serotonin (e.g., opioid drugs, SSRIs, SNRIs, benzodiazepines, tyramine) is not recommended. Monitor patients for hypertension with concomitant use.</td>
<td>The co-administration of ZEPOSIA with both a beta blocker and a calcium channel blocker has not been studied. However, there is a potential of additive effects on heart rate.</td>
<td>Treatment with ZEPOSIA should generally not be initiated in patients who are concurrently treated with both a heart-rate lowering calcium channel blocker (e.g., verapamil, diltiazem) and beta blocker (see Warnings and Precautions). If treatment initiation with ZEPOSIA is considered in patients on both a heart-rate lowering calcium channel blocker and beta blocker, advice from a cardiologist should be sought.</td>
</tr>
</tbody>
</table>

**Tyramine**

Table 4: Clinically Relevant Interactions Affecting ZEPOSIA When Co-administered with Other Drugs

<table>
<thead>
<tr>
<th>Prevention/Management</th>
<th>Clinical Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-administration of ZEPOSIA with strong CYP2C8 inhibitors should be avoided.</td>
<td>The co-administration of ZEPOSIA with both a beta blocker and a calcium channel blocker has not been studied. However, there is a potential of additive effects on heart rate.</td>
</tr>
</tbody>
</table>

**Use in Specific Populations**

**Pregnancy**

**Risk Summary**

There are no adequate data on the developmental risk associated with the use of ZEPOSIA in pregnant women.

- In animal studies, administration of ozanimod during pregnancy produced adverse effects on development, including embryolethality, an increase in fetal malformations, and neurobehavioral changes, in the absence of maternal toxicity. In rabbits, fetal blood vessel malformations occurred at clinically relevant maternal ozanimod and metabolite exposures (see Data). The receptor affected by ozanimod (sphingosine-1-phosphate) has been demonstrated to have an important role in embryogenesis, including vascular and neural development.
- In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

**Data**

**Animal Data**

Oral administration of ozanimod (0, 0.2, 0.6, or 2 mg/kg/day) to female rabbits during organogenesis resulted in a marked increase in embryofetal mortality, increased fetal malformations and skeletal variations (abnormal/destroyed ossification), and reduced fetal body weight at the highest dose tested. No maternal toxicity was observed. At the no-effect dose (1 mg/kg/day) for embryofetal effects (600 mg/day/kg) for embryofetal development; plasma ozanimod exposure (AUC) for ozanimod was approximately 60 times that in humans at the maximum recommended human dose (MRHD) of 0.2 mg/kg/day. Plasma AUCs for major human metabolites, CC112273 and CC1084037, were similar to and less than, respectively, those in humans at the MRHD.

Oral administration of ozanimod (0, 0.2, 0.6, or 2 mg/kg/day) to female rabbits throughout gestation and lactation resulted in a significant increase in the rate of hepatic malformations in litters born to ozanimod-treated maternal rabbits (see Data). The receptor affected by ozanimod (sphingosine-1-phosphate) has been demonstrated to have an important role in embryogenesis, including vascular and neural development. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

**Data**

**Animal Data**

Oral administration of ozanimod (0, 0.2, 1, or 5 mg/kg/day) to female rats during organogenesis resulted in a marked increase in embryofetal mortality, increased fetal malformations and skeletal variations (abnormal/destroyed ossification), and reduced fetal body weight at the highest dose tested. No maternal toxicity was observed. At the no-effect dose (1 mg/kg/day) for embryofetal effects (600 mg/kg/day) for embryofetal development; plasma ozanimod exposure (AUC) for ozanimod was approximately 60 times that in humans at the maximum recommended human dose (MRHD) of 0.2 mg/kg/day. Plasma AUCs for major human metabolites, CC112273 and CC1084037, were similar to and less than, respectively, those in humans at the MRHD.

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Perspectives From the Journey of the Patient With Rare Epilepsy

Joseph E. Sullivan, MD; Kelly Knupp, MD; Mary Anne Meskis; and Tracy Dixon-Salazar, PhD, share insight into the patient and provider journey of LGS and Dravet syndrome, from diagnosis through treatment.

By Matt Hoffman

Patients with rare epilepsies such as Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) often experience difficulties from the disease that extend beyond the symptoms and biological effects that immediately come to mind. In addition to burdens on quality of life, there can also be delays in diagnosis and difficulties with treatment success.

Currently, DS affects an estimated 1 of every 15,700 individuals, with approximately 80% to 90% of those having both an SCN1A mutation and a clinical diagnosis of DS.\(^1\) LGS, on the other hand, is estimated to occur in roughly 0.1 to 0.28 of every 1000,000 individuals, accounting for roughly 1% to 4% of all childhood epilepsy cases.\(^2\) Although these epilepsy disorders are rare, therapies are available to treat them, but many patients experience refractory disease, making the development of a treatment regimen a complex process. As the medical field moves toward more personalized and holistic care as a whole, the treatment process involves a much more in-depth conversation about the patient experience.

In a recent NeurologyLive\textsuperscript{®} Cure Connections\textsuperscript{®} series, a panel of experts in epilepsy care and advocacy came together to discuss how this landscape has shifted and to share their understanding of that patient experience from various angles. Moderated by Joseph E. Sullivan, MD, a professor of neurology at UCSF Weill Institute for Neurosciences, the conversation touched on a number of facets of the care paradigm.

 Syndrome Overview

**Dravet Syndrome**

Panel member Kelly Knupp, MD, a pediatric neurologist at Children’s Hospital Colorado, began the discussion with an overview of DS, noting that the developmental epileptic encephalopathy is often characterized by multiple seizure types provoked by temperature changes, as well as intellectual impairment. Notably, Knupp said, this impairment can become more apparent with age—a key change to look for diagnostically. DS can also be accompanied by progressive gait disorder and behavioral disorders, among other comorbidities.

“One of the characteristics of this syndrome is that it’s often associated with a pathogenic variant in a gene called SCN1A,” Knupp explained. “The vast majority of children do have one of those genetic diagnoses, but not all children. That’s important to keep in mind, as well [as the fact] that there’s a clinical syndrome, but we may not find a genetic mutation that goes along with it. It is also important to know that there are some children who have a pathogenic variant in SCN1A who don’t actually have Dravet syndrome. It’s important to look for both of those things: the clinical syndrome as well as the gene mutation.”

DS was initially believed to be more uncommon than it is, and recent epidemiological data suggest that missed diagnoses were prevalent in clinical practice prior to current advances in genetic testing.

**Lennox-Gastaut Syndrome**

Mary Anne Meskis, executive director of the Dravet Syndrome Foundation, added that LGS can be difficult to diagnose because it presents differently from other forms of childhood epilepsy and that it is often misdiagnosed as other conditions.

Tracy Dixon-Salazar, PhD, executive director of the Lennox-Gastaut Syndrome Foundation, pointed out that LGS is a particularly complex condition because it affects multiple areas of the brain and can be associated with significant learning disabilities and other neurodevelopmental disorders.

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**References**

1. [DS prevalence and genetics](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7964912/)
2. [LGS prevalence and genetics](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7609271/)
This was driven largely by a lack of understanding of DS itself, and Sullivan explained that during his training, he saw very few children with a diagnosis of DS. “It’s almost embarrassing, but you can see how it happens. We are told as pediatricians that febrile seizures are common and many of these kids are told not to worry about it.”

Knupp explained that in her practice, any child who has had a prolonged febrile seizure, particularly hemiclonal seizures, raises a flag. “I’m on the fence about the children who have had 2 simple febrile seizures and otherwise are doing well because we know that about one-third of children who have a first febrile seizure will go on to have a second febrile seizure. But, if there’s something like a prolonged seizure or a focal nature to the seizure, we have to consider doing genetic testing,” she said.

Sullivan added, “Age is a factor, too. We’re told that febrile seizures occur at 6 months; if a patient has a simple febrile seizure at 6 months and then another simple febrile seizure at 7 months, that’s a worry to me.”

Lennox-Gastaut Syndrome

In LGS, the diagnostic process is similarly challenging for a variety of reasons, though much of it is driven by controversy surrounding the clinical definition of the syndrome. Although criteria do exist to make the diagnosis, Knupp explained that LGS has numerous etiologies and often evolves from another status, making it challenging to catch and properly diagnose.

“To have a diagnosis of Lennox-Gastaut most people would agree that you should have multiple seizure types, maybe just 2, but at least 1 of those should be tonic seizures. There are characteristic EEG [electroencephalogram] patterns that should be seen with slow spike and wave and then also paroxysmal fast activity which is most often seen during sleep,” she said.

Additionally, children with LGS have, almost universally, intellectual impairment, Knupp continued. This is often considered a requirement for the diagnosis and can be accompanied by a time point for presentation—sometimes prior to the age of 11 years. However, she said, there are reports of individuals who presented during adolescence or in early adulthood with these signs and symptoms.

“Because this is a syndrome that most children evolve into, what’s important is that when our families are starting to develop multiple seizure types, we do take another look and repeat their EEG [electroencephalography] and look for the electrographic findings of this,” Knupp said. “There are certain patient populations that we should probably always be very sensitive to and probably be looking for evolution into the syndrome. There are definitely some high-risk patients that we should be looking for this diagnosis in, but we also have to keep in mind that’s not all of them, and this can happen to any one of our children who presents with childhood epilepsy. We always have to be aware of that and making sure that we are clarifying what seizure types are [being seen], what’s happening at night, and thinking about getting an EEG particularly in a child who is having multiple seizure types and has developed mental delay or intellectual impairment.”

Knupp and Sullivan detailed the list of genetic disorders that are frequently associated with LGS, noting that infantile spasms have one of the highest risks of evolving into LGS, especially in patients with refractory spasms. But those with an epilepsy risk factor, such as neonatal stroke or developmental brain abnormality, are an important secondary group to evaluate as well.

“You don’t necessarily present with Lennox-Gastaut; you present with a few seizures and then it takes some time for the syndrome to evolve and declare itself,” Sullivan said. “It’s our job as epilepsy providers to be aware of that evolution, not only EEG-wise—we don’t look at any of these things in isolation—but how the whole picture fits together. Then there is a third group where there are no epilepsy risk factors, and maybe even normal development, but they have their first few seizures and then very quickly evolve into the Lennox-Gastaut picture. You can always get even more narrow and say specific genetic diagnosis.”

We still have to work to educate our adult providers about the importance of getting a diagnosis and making sure that they know this testing is available and is significantly less costly than it was in the past.”

—MARY ANNE MESKIS

Patient Journey to Diagnosis

Dravet Syndrome

DS often presents during the first year of life, usually beginning with prolonged generalized tonic-clonic or hemiconvulsive seizures. Status epilepticus is also common among this population in the early stage of disease, and a variety of other seizures can occur prior to age 5 years. The disease itself is also often associated with hyperthermia, with the initial seizure often occurring alongside fever.

Recent advances in genetic testing have aided the diagnostic process, though many older patients previously experienced delays of several years prior to receiving an official diagnosis of DS. For one panel member, MARY ANNE MESKIS, executive director of the Dravet Syndrome Foundation, whose son is a patient with DS, the diagnostic delay was familiar.

“I think certainly in the last decade, we’ve really seen a change in the typical journey for patients and parents to get to diagnosis. Back then, my son, who is now 22, [did not receive a diagnosis] until age 4,” Meskis told the panel. “Early on, we kept being told that it was febrile seizures. Unfortunately, we still have some patients that follow that same diagnostic journey; if they’re not being seen by a health care professional that understands what they should be looking for and [one who] doesn’t order genetic testing, unfortunately it can still take several years until symptoms progress and until they find the right specialists that can help them get to diagnosis.”
For the physicians, though, the diagnosis can still be made without genetic testing. For experts in this realm of care, the key characteristics can be clear when a patient experiences an evolution from prolonged febrile seizures into multiple seizure types and temperature sensitivity. Additionally, in older patients, gait challenges can sometimes lead clinicians to the correct diagnosis. But as DS presents so early on, that time to see the evolution of seizures can be critical, and Sullivan noted that sometimes signs can be missed initially.

“The area where genetic testing has been really helpful has been with those very early seizures,” Knupp said. “It sometimes is challenging to tell the difference between a straightforward febrile seizure vs a febrile seizure associated with Dravet syndrome, particularly if it was not a hemiconvulsive seizure. But if I saw a patient whose first febrile seizure was a hemiconvulsive seizure on the right and their second febrile seizure was a hemiconvulsive seizure on the left, I would have felt really confident that it was Dravet syndrome, and that we should proceed as though that was the diagnosis.”

Sullivan added that without a proper childhood history of seizure evolution, oftentimes DS can be difficult to identify. Meskis echoed this sentiment, adding that as patients get older, unless the parent or guardian pushes for more answers, it can be particularly challenging to press for further inquiry into diagnosis, especially if the patient has improved otherwise.

“I have also heard from parents who kept pushing for testing, and after finally getting testing and a diagnosis, they might have had a child on a medication that was contraindicated for Dravet syndrome for many years,” Meskis said. “I think there’s a challenge and I think that we still have to work to educate our adult providers about the importance of getting a diagnosis and making sure that they know this testing is available and is significantly less costly than it was in the past, because that was a barrier for a long time for our families.”

Sullivan agreed, adding that the diagnosis also allows patients and families to experience a sense of community. Organizations such as the Dravet Syndrome Foundation and support groups provide a resource for these individuals living with similar day-to-day struggles. “I’ve just seen so much value in that,” he said.

**Lennox-Gastaut Syndrome**

In LGS, although the disease similarly presents early on in life, the situation can be less clear than with DS. This is mainly a result of the aforementioned lack of consensus about the clinical definition of LGS and the variety of underlying causes. Often, its cause goes completely unknown. For many, such as panelist **TRACY DIXON-SALAZAR, PHD**, executive director of the Lennox-Gastaut Syndrome Foundation, and whose daughter is a patient with LGS, the journey to diagnosis can take some time and can be characterized by numerous failed attempts at treatment.

This lag in diagnosis can lead to confusion for the parents and patients. Patients continue to experience seizures unexpectedly and without a discernable pattern, and all the while experiencing the consequences of these convulsive episodes without help from treatment. Over the past decade, though, the literature and understanding of LGS has improved drastically, which, in turn, has improved the diagnostic process for many. Cognitive changes in the setting of ongoing seizures, Knupp explained, are an immediate red flag to look into the possibility of LGS. Additionally, when it comes to disease management, a conversation about pairing nonpharmacologic interventions such as diet or stimulation devices can also provide some relief to patients.

“We are seeing a lot of families in our group that are coming in [for diagnosis at a] much younger [age]—1- or 1.5-year-olds, 2-year-olds that are getting in a lot earlier,” Dixon-Salazar said. “Our understanding is that there is this evolution and…that it is not the doctors who are failing you, it is the treatments. Science and medicine have not got to the point where they can help in a lot of ways, but you don’t want to stop trying. Families are supported now by other caregivers who have been there, done that, so I definitely think [the diagnostic journey] is faster and better.”

Dixon-Salazar added that part of the difficulty in the diagnostic process is that many patients with LGS are being treated in general neurology or family medicine practices, which may be unfamiliar with the rare epilepsy, marking the importance of getting referrals to epileptologists, such as Knupp or Sullivan. From there, Dixon-Salazar said, patients and their families can more easily find hope for their future care.

“That first visit is often trying to provide some education, understand what’s going on so far, and set reasonable expectations, which is part of our job to be able to move forward,” Knupp explained. “That first visit is usually assessing how many medications have been tried and having that conversation that if you have failed 2 or more medications, the likelihood of more medicine making you seizure free is pretty low.”

“The truth is, up until 2000, that wasn’t our expectation. We thought, we will just keep trying medications and we will eventually find something that works for you, and that has changed our conversation. It’s hard for families to hear that, but it sets the framework for us to do reasonable goal-setting so that we can say, ‘You’ve reached the point where it’s unlikely a medicine will make you seizure free.’ It doesn’t mean that we are not going to try, and we have lots of options to look at to get there, but let’s talk about reasonable goals for the next couple of months. Maybe that’s finding a good balance between medications and adverse effects rather than pushing medicines that make somebody so sedated that their quality of life is poor,” Knupp said.

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go to neurologylive.com/ds-lgs-patient-journey

For a full list of references, see the article on NeurologyLive.com.
PXT3003 Aims to Become First Approved Therapeutic for Charcot-Marie-Tooth Disease

Following positive phase 3 findings, a second study featuring more than 300 patients will aim to confirm PXT3003’s effect in patients with Charcot-Marie-Tooth disease type 1a.

By Marco Meglio

PXT3003 (PHARNEXT SA), a novel fixed-dose synergistic combination of baclofen, naltrexone, and sorbitol, is being evaluated in the pivotal phase 3 PREMIER study (NCT04762758) of patients with Charcot-Marie-Tooth disease type 1a (CMT1A), a neurological disease for which there are no curative or symptomatic medications approved. The international, randomized, double-blind, 2-arm, placebo-controlled trial is taking place in 52 centers across the United States, Canada, Europe, and Israel, with topline data expected to be announced in Q4 2023.1

CMT1A, the most common form of CMT, is caused by a duplication of the PMP22 gene that is responsible for the production of the peripheral myelin sheath protein. Its duplication leads to abnormal levels of PMP22 protein, which then leads to a failure in the production of normal myelin. In data from preclinical studies, PXT3003 was shown to suppress PMP22 production and improve neuromuscular function.

In PREMIER, approximately 350 patients will be randomly assigned to either PXT3003 or placebo for a 15-month treatment period, with changes in score on the Overall Neuropathy Limitations Scale (ONLS), a measure of functional motor disability, serving as the primary end point. Along with safety, there are several secondary end points, including the 10-Meter Walk Test, Patient Global Impression of Severity score, Patient Global Impression of Change score, Charcot-Marie-Tooth Neuropathy Score version 2, and quantified muscular testing for hand grip and bilateral foot dorsiflexion dynamometry.

The dose of PXT3003 tested in PREMIER corresponds to the high dose tested in the pivotal phase 3 trial, PLEO-CMT (NCT02579759). That study randomly assigned 323 individuals with mild to moderate CMT1A to either 5 mL of high- or low-dose PXT3003 or placebo, twice daily for up to 15 months, with change in ONLS score at 12 and 15 months as the primary end point. The high-dose treatment arm was prematurely stopped in September 2017 because of an unexpected formulation issue, after which the FDA and European Medicines Agency requested an additional phase 3 study to confirm the efficacy and safety of PXT3003, leading to PREMIER.2

In PLEO-CMT, a revised statistical analysis plan was developed to consider the high amount of missing data because of the discontinuation of patients in this treatment arm. At the trial’s end, both high- and low-dose PXT3003 groups demonstrated decreased scores on the ONLS, indicating disability improvement, whereas those receiving placebo had worsening disability progression. The change in ONLS score was greatest in the high-dose group, for which the mean effect was –0.37 points (P = .008). Between the low-dose and placebo groups, the mean effect was not statistically significant (P = .287).

The open-label extension of that study, PLEO-CMT-FU, had results announced in May 2022, which further confirmed the long-term safety and effectiveness of PXT3003 over a 5-year treatment period. The data readout included patients who had 15 months in PLEO-CMT; followed by 9 months in period 1 of PLEO-CMT-FU and 36 months of period 2 in the same extension study.3

After showing a change of –0.11 in ONLS score at 15 months, patients in the high-dose PXT3003 group had an additional mean improvement of –0.17 in the following 45 months. The low-dose group didn’t see as much efficacy signal, but still had improvements of –0.17 in ONLS score in the final 45 months of treatment, following a –0.05 change seen at the 15-month mark. Notably, among patients receiving placebo in the original 15-week period who then switched to low-dose or high-dose PXT3003 during period 1 and high dose during period 2, the mean change in ONLS score was –0.11 in the final 45 months compared with a worsening change of 0.17 in the original 15-week treatment period.

Following the data announcement, Shahram Attarian, MD, PhD, head of the Neuromuscular Diseases Service and ALS Department at Timone Hospital in Marseilles, France, said in a statement that “as an investigator involved since the beginning in the clinical development of PXT3003 in CMT1A, I find these long-term safety and efficacy data very encouraging. Being able to stabilize, or even improve, patients with CMT1A is an extremely worthwhile goal, particularly as these individuals will inevitably decline following the long-term natural course of the disease with the currently available standard of care.”4 Attarian, who served as lead investigator for PLEO-CMT and PLEO-CMT-FU, currently serves as lead investigator of the PREMIER trial.

For a full list of references, see the article on NeurologyLive.com.
Pediatric Sleep Disorders: Assessment and Treatment

By Yolanda A. Yu, DO; and Alon Y. Avidan, MD, MPH

Division of Pediatric Pulmonology and Sleep Medicine, Department of Pediatrics, University of California, Los Angeles. Department of Neurology, University of California, Los Angeles

SLEEP PLAYS A FUNDAMENTAL ROLE in human development and a critical role in the health of children. Unfortunately, sleep problems are often underappreciated and unrecognized in pediatric neurology, despite the pervasive nature of sleep complaints and their high prevalence—estimated at 10% to 46.4% of school-aged children.1-3 Untreated sleep problems result in functional impairment in children and may have long-term consequences.

In this review, we discuss common pediatric sleep disorders and provide epidemiology background, clinical presentation, diagnostic evaluation, and management opportunities.

General Approach in Evaluating Children With Sleep Disturbances

The general assessment of pediatric sleep disorders must, at a minimum, include survey questions about sleep duration and regularity, bedtime resistance and sleep onset delay, night waking, symptoms of sleep-disordered breathing, and signs of increased daytime sleepiness. A sleep diary is of fundamental importance in capturing these data and can be downloaded from a sleep education website endorsed by the American Academy of Sleep Medicine (AASM) or directly from the AASM at sleepereducation.org/resources/sleep-diary.

Multiple brief sleep screening questionnaires have been developed and validated, including BEARS, a 5-item assessment that is the acronym for the following important areas to screen: bedtime issues, excessive daytime sleepiness, night awakenings, regularity and duration of sleep, and snoring.4

Obstructive Sleep Apnea Syndrome

Pediatric obstructive sleep apnea syndrome (OSAS) is a sleep-related respiratory disorder characterized by intermittent partial or complete upper airway obstruction, which disrupts sleep architecture, impairs ventilation, and impacts brain development.5-6 Its prevalence is estimated to be 1% to 4% of children, although a higher prevalence is seen in certain pediatric populations such as children with trisomy 21, cleft palate, and craniofacial syndromes.7-10 Although pediatric OSAS can occur in all age groups, there are 2 peak periods. The first peak, in preschool-aged children, is associated with adenotonsillar hypertrophy.6 The second peak, in adolescents, is associated with obesity.5 There is no sex difference in the prevalence of pediatric OSAS in prepubertal children, although higher prevalence is seen in adolescent boys than in adolescent girls.8,11 Multiple risk factors are associated with pediatric OSAS (TABLE 15,12,11).
Obesity, adenotonsillar hypertrophy, craniofacial abnormalities

**Consequences of Untreated Pediatric OSAS**

Male sex

Daytime sleepiness, hyperactivity, inattention, and aggressiveness

Risk Factors for Pediatric OSAS

Cerebral palsy, neuromuscular disorders

Continuous positive airway pressure therapy may be considered in pediatric patients with mild OSA for whom adenotonsillectomy is contraindicated or in pediatric patients with mild OSA that persists following adenotonsillectomy. Topical intranasal corticosteroids may be considered in select pediatric patients with mild OSA who are overweight or obese. Left untreated, pediatric OSAS is associated with behavioral, cardiovascular, and neurocognitive consequences, as well as impaired growth and development (**TABLE 2**). *NeurologyLive.com*  

Behavioral Insomnia of Childhood

Insomnia is a sleep disorder characterized by chronic difficulty initiating and maintaining sleep despite adequate opportunity for sleep, resulting in daytime impairment. Its prevalence ranges from 19.3% to 41% in children, with the highest prevalence seen in girls aged 11 to 12 years.  

Behavioral insomnia of childhood (BIC) is one type of insomnia delineated in the *International Classification of Sleep Disorders* (2nd ed). Within this category of insomnia are 3 subtypes: sleep-onset association type, limit-setting type, and combined type.

1. **BIC sleep-onset association type** is characterized by dependence on specific conditions to initiate sleep or return to sleep following nighttime awakenings. In the absence of these specific conditions, sleep onset is delayed. This type may also present with frequent or prolonged nighttime awakenings, which often require caregiver or parental intervention.

2. **BIC limit-setting type** is characterized by bedtime refusal or bedtime stalling and is thought to result from inadequate limit setting by the caregiver or parent. Bedtime refusal presents as refusal to get ready for bed, go to bed, or stay in bed, and bedtime stalling manifests as attempts to delay bedtime. In BIC limit-setting type, sleep onset is often delayed, although there are no frequent or prolonged nighttime awakenings.

3. **BIC combined type** has features of both BIC sleep-onset association type and BIC limit-setting type.

Diagnosis of BIC is based on parental or caregiver report of symptoms. Polysomnography is not typically performed as part of the diagnostic work-up for insomnia, unless it is suspected that part of the stalling to get in bed is associated with leg pain (growing pains mistaken for restless legs syndrome). Other useful diagnostic tools include a sleep diary or sleep log and sleep questionnaires.

The AASM recommends behavioral interventions for the treatment of bedtime problems and nighttime awakenings in children younger than 5 years. The specific therapies recommended include unmodified extinction, extinction with parental presence, graduated extinction, delayed bedtime with removal from bed or positive bedtime routines, scheduled awakenings, and parent education and prevention. These behavioral interventions are associated with decreases in bedtime resistance and nighttime awakenings.

Untreated BIC affects not only children with BIC, but also their caregivers. In children, insufficient sleep and sleep difficulties are associated with attention-deficit/hyperactivity disorder, as well as poorer executive functioning, behavior, and social-emotional functioning. Parents of infants with BIC sleep-onset association type experience sleep deprivation, depression, and decreased marital intimacy.

**Pediatric Narcolepsy**

Narcolepsy is a central disorder of hypersomnolence, with an estimated prevalence ranging from 0.23 per 100,000 in Israel to 160 per 100,000 in Japan. The annual incidence in Finnish patients younger than 17 years is approximately 0.12 to 5.3 per 100,000. There is a bimodal peak for

**TABLE 1.** Risk Factors for Pediatric OSAS

<table>
<thead>
<tr>
<th>Assigned sex</th>
<th>Male sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noisy breathing</td>
<td>Snoring &gt;3 months</td>
</tr>
<tr>
<td>Anatomy</td>
<td>Obesity, adenotonsillar hypertrophy, craniofacial abnormalities</td>
</tr>
<tr>
<td>Neurologic conditions</td>
<td>Cerebral palsy, neuromuscular disorders</td>
</tr>
<tr>
<td>Metabolic storage disease</td>
<td>Mucopolysaccharidosis</td>
</tr>
<tr>
<td>Hematopoietic</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Gastrointestinal and feeding</td>
<td>Breastfeeding, gastroesophageal reflux</td>
</tr>
<tr>
<td>Environmental</td>
<td>Environmental tobacco smoke exposure</td>
</tr>
</tbody>
</table>

OSAS, obstructive sleep apnea syndrome.

**TABLE 2.** Consequences of Untreated Pediatric OSAS

| Cardiovascular | Systemic hypertension, pulmonary hypertension, and cor pulmonale |
| Behavioral | Daytime sleepiness, hyperactivity, inattention, and aggressiveness |
| Neurocognitive | Impairments in general intelligence (including IQ), executive functioning, mathematical abilities, academic performance, concept formation, learning, memory, and verbal and nonverbal comprehension |

OSAS, obstructive sleep apnea syndrome.
age of onset, with the first peak occurring at age 15 years and the second peak occurring at age 35 years.28 Diagnosis is often delayed in pediatric patients by 10 to 15 years due to misdiagnosis with other disorders such as depression, hypothyroidism, "laziness," and conversion disorder.26

Narcolepsy is categorized into 2 phenotypes—narcolepsy type 1 (NT1, previously narcolepsy with cataplexy) and NT2 (previously narcolepsy without cataplexy). Both subtypes are characterized by excessive daytime sleepiness (EDS). EDS commonly presents as inability to maintain alertness and wakefulness during the day and inability to maintain sleep during the night, although in children it may manifest as excessively long sleep duration or need for daytime naps that had previously stopped.33

NT1 is characterized by the presence of cataplexy and hypocretin (orexin) deficiency, which is absent in NT2. Cataplexy presents with brief episodes of abrupt loss of muscle tone without loss of consciousness and is typically triggered by strong emotions such as laughter and surprise. Children may have catapletic facies, which manifests as mouth opening, tongue protrusion, and ptosis. Other associated features include hypnagogic hallucinations, hypnopompic hallucinations, sleep paralysis, and unexplained excessive weight gain. Hypnagogic and hypnopompic hallucinations typically occur during sleep-wake transitions and usually have visual, auditory, and tactile components. Sleep paralysis presents as a transient inability to move voluntary muscles except for eye movements and breathing. REM sleep behavior disorder (RBD) and REM sleep without atonia are associated with narcolepsy in children and may occur prior to the onset of narcolepsy symptoms. Unlike the adult phenotype of RBD, there is no established risk of phenocconversion to α-synucleinopathy. NT1 is associated with brain hypocretin deficiency (if it is measured). It is also associated with the presence of human leukocyte antigen (HLA) subtype DQB1*0602, although this HLA subtype can be present in up to 30% of individuals without narcolepsy.33

The diagnostic work-up often includes actigraphy or a sleep diary, a nocturnal polysomnogram, and a multiple sleep latency test (MSLT) the day after the polysomnogram. The AASM recommends at least 1 week of actigraphy recording with an accompanying sleep log prior to the MSLT to exclude circadian rhythm disorders, shift work disorder, and insufficient sleep disorder as possible etiologies for EDS.34 Testing must occur after correction of sleep apnea, sleep deprivation, and sleep-wake circadian disorders. The nocturnal polysomnogram should be performed the night prior to the MSLT to confirm sufficient sleep duration and measurement of REM sleep latency.34 Antidepressants and other medications that affect REM sleep must be discontinued for at least 2 weeks prior to the MSLT.33 Additional testing may include HLA typing for HLA DQB1*0602, and measurement of cerebrospinal fluid levels of hypocretin-1.33

Management includes both behavioral and pharmacologic treatment. Planned daytime naps are recommended to improve sleepiness.29 Other nonpharmacologic treatments include adherence to good sleep hygiene, consistent sleep schedule with adequate sleep duration, regular physical activity, and avoidance of emotional triggers for cataplexy.36 A limited number of pharmacologic options are available for pediatric patients. The AASM recommends the use of modafinil (Provigil; Cephalon) or sodium oxybate (Xyrem; Jazz) in pediatric patients with narcolepsy.37 However, the FDA currently lists sodium oxybate for the treatment of excessive sleepiness and cataplexy (for patients aged 7-17 years), oxybate salts (a low-sodium version of sodium oxybate) for the treatment of excessive sleepiness and cataplexy (aged 7-17 years), and traditional stimulants for management of daytime sleepiness associated with narcolepsy.

**Parasomnias**

Parasomnias are abnormal behavioral events or experiences that occur during sleep onset, sleep transitions, or arousals from sleep (TABLE 3).38 They are classified into REM-related parasomnias, non-REM (NREM)-related parasomnias, and other parasomnias. Parasomnias are common occurrences in the pediatric population, with an estimated prevalence as high as 84% among those between 2 and 6 years old.39 The most frequently encountered parasomnia is somniloquy (sleep talking).39 Other commonly encountered pediatric parasomnias are sleep terrors, sleep enuresis, and somnambulism (sleepwalking).39 Confusional arousals, recurrent isolated sleep paralysis, and nightmare disorder are also described in pediatric patients.38

**TABLE 3. Types of Parasomnias**38

<table>
<thead>
<tr>
<th>NREM-related parasomnias, disorders of arousal</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Confusional arousals*</td>
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<tr>
<td>- Sleepwalking* (sleep-related eating-disorder subtype)</td>
</tr>
<tr>
<td>- Sleep terrors</td>
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</tbody>
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<table>
<thead>
<tr>
<th>REM-related parasomnias</th>
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</thead>
<tbody>
<tr>
<td>- REM sleep behavior disorder (including RSWA in pediatric narcolepsy)</td>
</tr>
<tr>
<td>- Recurrent isolated sleep paralysis</td>
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<tr>
<td>- Nightmare disorder</td>
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</table>

<table>
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<tr>
<th>Other parasomnias</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Exploding head syndrome</td>
</tr>
<tr>
<td>- Sleep-related hallucinations</td>
</tr>
<tr>
<td>- Sleep enuresis*</td>
</tr>
<tr>
<td>- Parasomnia due to a medical disorder</td>
</tr>
<tr>
<td>- Parasomnia due to a medication or substance</td>
</tr>
<tr>
<td>- Parasomnia, unspecified</td>
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</table>

<table>
<thead>
<tr>
<th>Isolated symptoms and normal variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sleep talking</td>
</tr>
</tbody>
</table>

NREM, non-REM; RSWA, REM sleep without atonia.
*Common in pediatrics.

Parasomnias are diagnosed based on clinical history. Although polysomnography is not routinely indicated for evaluation of uncomplicated parasomnias, it may be useful to evaluate for other sleep disorders such as obstructive sleep apnea, identify potential triggers, and rule out disorders with similar clinical manifestations such as nocturnal seizures.38 Treatment is dependent on the specific type of parasomnia involved. General management strategies for NREM-related parasomnias are parental reassurance, promotion of a safe sleep environment (such as avoiding bunk beds for those who sleep walk), appropriate sleep hygiene, and avoidance of potential triggers such as environmental...
disruptions, sleep deprivation, and stress. Caregivers should be counseled to avoid intervention during the parasomnia because this could worsen the event. If the NREM-related parasomnias occur frequently and predictably, scheduled awakenings may be considered. In this management strategy, the pediatric patient is woken up 15 to 30 minutes prior to the time when the parasomnia typically occurs. This is done nightly for 2 to 4 weeks until resolution. Pharmacologic treatment is not routinely indicated in the management of NREM-related parasomnias unless these events are severe, occur frequently, or may result in injuries. Medications are often used off label and include benzodiazepines and tricyclic antidepressants.

**Sleep-Related Epilepsy**

Sleep-related epilepsy encompasses multiple epileptic syndromes that occur predominantly during sleep or following arousals from sleep. If there is concern for epilepsy, a standard daytime 16-channel to 20-channel electroencephalogram (EEG) or ambulatory 24-hour EEG monitoring should be considered. For nocturnal frontal lobe epilepsy or sleep-related hypermotor epilepsy, nocturnal polysomnogram utilizing expanded EEG montage and high definition video is the gold standard for diagnosis.

Treatment is dependent on the specific epileptic syndrome diagnosed. General treatment strategies include avoidance of seizure triggers (such as sleep deprivation) and adherence to an antiepileptic drug. Sleep disorders that disrupt sleep should be treated to improve seizure control.

**Circadian Rhythm Sleep-Wake Disorder**

Circadian rhythm sleep-wake disorders (CRWSDs) result from disruptions to the intrinsic circadian rhythm. The majority of CRWSDs are a consequence of misalignment of the innate circadian rhythm and the desired sleep-wake schedule. This disturbance in circadian rhythm presents as excessive sleepiness and difficulty with sleep initiation and maintenance, as well as functional impairment.

The AASM delineates 7 types of CRSWD. Of these, the most common CRSWD in pediatrics is delayed sleep-wake phase disorder (DSWPD), with an estimated prevalence of 3.3% to 8.4% in adolescents, with a slight predominance in girls. DSWPD is characterized by a consistent delay in sleep-onset time relative to conventional time, difficulty with sleep initiation at the conventional bedtime, and difficulty awakening at the conventional wake time. The delay in sleep onset is typically 2 hours or more. Those with DSWPD who can follow their preferred schedule typically have normal sleep quality and sleep duration, although timing is delayed.

The diagnostic work-up includes detailed sleep history, sleep log, and actigraphy recording (when possible) for at least 7 days (preferably 14 days). Standardized chronotype questionnaires may be considered to assess for morningness and eveningness. Laboratory studies demonstrating delay in circadian rhythm may be used to confirm the diagnosis, such as dim-light melatonin onset or urinary 6-sulfoaxymelatonin. Polysomnography is not routinely indicated for diagnosis.

Treatment involves both pharmacologic and nonpharmacologic interventions. For pharmacologic interventions, the AASM recommends the use of strategically timed exogenous melatonin administration, although long-term data on melatonin in pediatric patients are lacking. For nonpharmacologic treatment, the AASM recommends postawakening light therapy in conjunction with behavioral interventions. Left untreated, DSWPD negatively impacts academic performance, social functioning, and caregiver well-being.

**Restless Legs Syndrome**

Restless legs syndrome (RLS) is a sleep-related movement disorder seen in 1.9% to 2.0% of pediatric patients. This sensorimotor disorder is characterized by an urge to move the legs that is associated with an uncomfortable or unpleasant sensation. These symptoms occur primarily at night, worsen during inactivity or rest, and improve with movement. Common complaints include disturbed sleep, daytime fatigue, and daytime sleepiness. Pediatric RLS is associated with iron deficiency, attention-deficit/hyperactivity disorder, anxiety, depression, oppositional defiant disorder, parasomnias, and chronic kidney disease. It is also associated with gene variants of BTBD9, MEIS1, MAP2K5/LBXCOR, and PTPRD. The presence of RLS in a first-degree relative is a risk factor for RLS.

RLS is diagnosed clinically, but it can be challenging to diagnose because it requires pediatric patients to describe their symptoms in their own words. Several diagnostic tools have been developed specifically for pediatric RLS including the pediatric Emory RLS diagnostic questionnaire and the RLS questionnaire. Severity and quality-of-life questionnaires have also been developed specific to pediatric RLS. Polysomnography is not typically indicated in the diagnosis of RLS, but it may demonstrate periodic limb movements of sleep, elevated arousal index, and sleep abnormalities.

Management of pediatric RLS includes both pharmacologic and nonpharmacologic treatment. Nonpharmacologic interventions include the establishment of good sleep habits, physical activity, and avoidance of RLS exacerbating factors, such as inadequate sleep, irregular sleep schedule, pain, caffeine, nicotine, alcohol, and medications (sedating antihistamines, neuroleptics, and serotonergic antidepressants). Pharmacologic treatment options are limited in pediatric RLS and include iron supplementation, clonidine, and gabapentin.

**Sleep and COVID-19**

The COVID-19 pandemic has affected many aspects of pediatric health, including sleep. Findings from multiple studies have demonstrated changes in sleep patterns in both preschool-aged children and adolescents, particularly in delayed sleep timing. During the pandemic, Chinese preschoolers displayed later bedtimes and wake times, shorter nap duration, and longer nocturnal sleep duration. Caregivers also reported fewer sleep disturbances. Adolescents in the United States were noted to have increased difficulties initiating and maintaining sleep, later bedtimes and wake times, longer school-night sleep duration, and less daytime sleepiness during the pandemic. Other study data have demonstrated shifts in sleep timing but have not supported changes in sleep duration. Worsening in sleep quality has also been demonstrated in school-aged children during the pandemic.

For a full list of references, see the article on NeurologyLive.com.
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**RESEARCH AWARDS**

**Research Pair Receive Joint Alzheimer Award**
The *Journal of Alzheimer’s Disease* named Yonas E. Geda, MD, MSc, and Janina Krell-Roesch, PhD, joint recipients of the 2022 Alzheimer Award for their research on physical activity and modifying aspects of cognitive function. Geda, a neuropsychiatrist and behavioral neurologist at Barrow Neurological Institute, and Krell-Roesch, an investigator at Karlsruhe Institute of Technology, each received a bronze medal and cash prize of $7500 as part of their winnings. The duo’s research included a longitudinal population-based study that followed 2060 cognitively unimpaired individuals who reported their physical activity level in midlife and in late life as part of the Mayo Clinic Study of Aging. The findings showed that older adults experience a decline in global and domain-specific cognitive function over time; however, in those who were engaging in physical activity, this decline was less pronounced.

**INSTITUTION INITIATIVES**

**Grant to Miller School of Medicine Helps Fund Major Genetic Study of Alzheimer Disease**
The John P. Hussman Institute for Human Genomics (HIHG) at the University of Miami Miller School of Medicine in Florida will lead a 5-year, international, multisite initiative with several other notable universities geared toward improving overall knowledge on genetic associations between Alzheimer disease and individuals of Hispanic and African ancestry. Powered by a $46 million grant from the National Institute on Aging, the domestic and international sites will be overseen by Margaret A. Pericak-Vance, PhD, director of the HIHG, and professor and executive vice chair of the Dr. John T. Macdonald Foundation Department of Human Genetics. The multisite enterprise will help to bridge the research disparities that have historically existed in diverse communities. Through the recruitment, assessment, and genetic analysis of a significantly large cohort of participants of Hispanic/Latinx and African ancestries, clinical, phenotypic, and genetic data, along with social determinants of health factors, will be collected to create a large genomic study resource.

**Ochsner Medical Center Earns Most Demanding Stroke Certification**
Following a rigorous, unannounced onsite review in April 2022, Ochsner Medical Center in New Orleans, Louisiana, was awarded The Joint Commission’s Gold Seal of Approval and the American Stroke Association Heart-Check mark for Comprehensive Stroke Center certification. The advanced Comprehensive Stroke Center certification is the most demanding stroke certification and is designed for hospitals that have specific abilities to receive and treat the most complex stroke cases. Ochsner has held the certification for the past 9 years. During the onsite review, program management and the center’s ability to facilitate and deliver surgical and clinical care of patients with stroke was evaluated to see whether they met certification standards. These standards had been previously developed in consultation with health care experts and providers, measurement experts, and patients.

**Goizueta Foundation Commitment Helps Establish Emory University Brain Disease Center**
After Emory University established their new Brain Health Personalized Medicine Institute in May 2021, the Goizueta Foundation committed $50 million to the center, which has been renamed Goizueta Institute at Emory Brain Health. The institute plans to leverage the power of large-scale data collection and analysis with patients and the health care community to predict, prevent, diagnose, and treat brain disease. Olga Goizueta Rawls, chair and CEO of The Goizueta Foundation, said in a statement, “Emory has been a leader in the development of science and technology for the prevention and treatment of brain disease. The Goizueta Foundation is proud to help bring these innovations into clinical practice to promote healthy aging.” A few key goals of the institute moving forward include developing a data technology platform, identifying brain disease at the earliest stage possible, and establishing a repository for biospecimens to fuel the development and application of the next generation of biomarkers.

**AT THE HELM**

**Shulman Is Named Codirector of Texas Children’s Hospital**
Joshua M. Shulman, MD, PhD, a neuroscientist and adult neurologist with more than 25 years of experience, has been named as the new codirector of the Jan and Dan Duncan Neurological Research Institute (NRI) at Texas Children’s Hospital in Houston. He is also founding director of Baylor College of Medicine Center for Alzheimer’s and Neurodegenerative Diseases, and holds the Huffington Foundation Endowed Chair for Parkinson’s Disease Research at Duncan NRI and the Effie Marie Cain Chair in Alzheimer’s Disease Research at Baylor University. “The Duncan NRI truly is a special place, with an unparalleled collaborative and cross-disciplinary approach that propels groundbreaking research on brain diseases affecting children and adults alike. The success of my research program over the last decade owes much to the Duncan NRI and I am proud to serve as its codirector,” Shulman said in a statement.
Every day, people with Parkinson's face a challenging opponent. Yet, members of this amazing community strive to follow their passions undeterred, refusing to let Parkinson's define them. That fighting spirit inspires our resolve to work towards innovative new therapies. At Supernus, we're proud to partner with the community, and to share some of the iconic ways people with PD strive to live their best lives today and every day.