Sleep Deprivation Among Frontline Health Care Workers During COVID-19 Turns Critical

Data Evolution in Alzheimer Disease: Is the Future Digital?
BY NICOLA DAVIES, PHD

A Team Approach to Asleep Deep Brain Stimulation
BY JASON M. SCHWALB, MD;
ELLEN L. AIR, MD, PHD;
NEEPA J. PATEL, MD; AND JULIA A. WALL

RGMa Inhibition for Repair and Protection in Multiple Sclerosis
BY JENNIFER S. SUN, PHD

CLINICAL VIEWPOINT
The Global Push for Mechanical Thrombectomy in Stroke Care
WITH DILEEP YAVAGAL, MD

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HOW DO YOU KNOW IF MCI IS LIKELY TO PROGRESS TO AD DEMENTIA?

- **COGNITIVE ASSESSMENT:** Elevated subjective memory complaints; MMSE=28/30; re-evaluation after continued complaints, MoCA=25/30

- **STAGES OF AD PROGRESSION:**
  - Preclinical
  - Mild AD Dementia
  - Moderate AD Dementia
  - Severe AD Dementia

- **DIAGNOSIS:** MCI due to AD

- **BIOMARKER CONFIRMATION:** Amyloid-positive

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**References:**

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See how Aβ testing can help confirm AD pathology at identifyalz.com.
HOW DO YOU KNOW IF MCI IS LIKELY TO PROGRESS TO AD DEMENTIA?

Until recently, the diagnosis of Alzheimer’s disease (AD) was almost solely based on clinical evaluation. And the average time to diagnosis has been 2 to 3 years after symptom onset.1 But diagnosis of AD may be ready to evolve.

AD is thought to be caused by a cascade of neurological damage triggered by the accumulation of amyloid beta (Aβ).2 These Aβ aggregates can serve as a biological marker of AD pathology, and may help inform the diagnosis and management of the first symptomatic stage of AD: mild cognitive impairment (MCI) due to AD.3,4

Currently used in cutting-edge investigational research, biomarker confirmation of Aβ via positron emission tomography (PET) scan or cerebrospinal fluid (CSF) test is beginning to move into clinical practice.3,5-8

The diagnostic value of ascertaining AD as the cause of MCI is that the clinician can intervene before greater neuronal damage occurs and more cognition and function are lost.4

Recently, the large-scale IDEAS Study (N=11,409) showed the utility of Aβ confirmation to inform appropriate care, which led to changes in the management of over 60% of MCI patients and ~64% of patients with dementia.9

With the potential for Aβ testing to impact the management of AD, and other biomarker tests on the horizon, advances in AD diagnostics offer hope that diagnosing AD at the MCI stage may become the standard of care and improve the management of Alzheimer’s disease.10

MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; IDEAS=Imaging Dementia—Evidence for Amyloid Scanning.

Sleep Deprivation Among Frontline Health Care Workers During COVID-19 Turns Critical

BY LINDA PECKEL

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Coming Together Amid Unique Challenges

THE MEDICAL COMMUNITY HAS BEEN pitted against once-in-a-generation adversity in 2020, as the effects of an ongoing global pandemic have stretched to all corners of medical practice. Nevertheless, many physicians have risen to the challenge with fortitude, as evidenced by the incredible work being done in hospitals, labs, and institutions around the country and the rest of the world. Despite their efforts, though, those working in health care have felt the pandemic’s impact.

In this issue of NeurologyLive®, the cover story on page 22 offers insight into some of those ripples of the pandemic, including the currently critical state of sleep deprivation among those working on the front line. The pandemic's effect on sleep has been universal, according to experts, and is becoming a vital issue that needs to be addressed.

With guidance from guest editor in chief Karl Doghramji, MD, professor of psychiatry, neurology, and medicine at Thomas Jefferson University, where he also serves as medical director of the Jefferson Sleep Disorders Center and program director of the Fellowship in Sleep Medicine, we explore this challenge in depth. Doghramji also notes that despite this year’s uphill battle, the neurology community has witnessed a number of advances in sleep medicine, particularly in insomnia.

The progress in science has continued elsewhere, with advances in Alzheimer disease poised to make waves. In addition to the potential upcoming approval of aducanumab, the evolution of digital biomarkers offers the chance to revolutionize the diagnosis and treatment of the disease. This transformation is explored in detail on page 47.

Those treating patients in neurology have also proved they can come together in these times of peril, translating the ongoing conversations around collaboration in the field into practice. This is apparent in a feature on page 56, in which Jason M. Schwalb, MD; Ellen L. Air, MD, PhD; Neepa J. Patel, MD; and Julia A. Wall, of Henry Ford Health System, highlight how their team approach to deep brain stimulation can provide the best care for patients.

In that same cooperative breath, this issue's Clinical Viewpoint, on page 43, features a call to the clinical community for further utilization of mechanical thrombectomy from Dileep R. Yavagal, MD, professor of clinical neurology at the University of Miami. He discusses how the Mechanical Thrombectomy 2020+ initiative he is chairing through the Society of Vascular and Interventional Neurology seeks to increase global access to the procedure.

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 editor Matt Hoffman at mhoffman@neurologylive.com.

Thank you for reading.

Mike Hennessy Sr
Chairman and Founder
MJH Life Sciences™
FINTEPLA is indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older.

**INDICATIONS AND USAGE**

FINTEPLA is indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older.

**IMPORTANT SAFETY INFORMATION**

**BOXED WARNING: VALVULAR HEART DISEASE and PULMONARY ARTERIAL HYPERTENSION**

- There is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease and pulmonary arterial hypertension.
- Echocardiogram assessments are required before, during, and after treatment with FINTEPLA.
- FINTEPLA is available only through a restricted program called the FINTEPLA REMS.

**CONTRAINDICATIONS**

FINTEPLA is contraindicated in patients with hypersensitivity to fenfluramine or any of the excipients in FINTEPLA and with concomitant use of, or within 14 days of, the administration of monoamine oxidase inhibitors because of an increased risk of serotonin syndrome.

**WARNINGS AND PRECAUTIONS**

Valvular Heart Disease and Pulmonary Arterial Hypertension (see Boxed Warning): Because of the association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease and pulmonary arterial hypertension, cardiac monitoring via echocardiogram is required prior to starting treatment, during treatment, and after treatment with FINTEPLA concludes. Cardiac monitoring via echocardiogram can aid in early detection of this condition. In clinical trials of up to 3 years in duration, no patient receiving FINTEPLA developed valvular heart disease or pulmonary arterial hypertension.

**ADVERSE REACTIONS**

The most common adverse reactions (incidence at least 10% and greater than 1%) are:

- Somnolence, sedation, and lethargy
- Diarrhea
- Decreased appetite
- Headache
- Fatigue
- Anorexia
- Increase in Blood Pressure
- Glaucoma
- Orthostatic hypotension
- Edema

**MONITORING:**

Prior to starting treatment, patients must undergo an echocardiogram to evaluate for valvular heart disease and pulmonary arterial hypertension. Echocardiograms should be repeated every 6 months, and once at 3-6 months post treatment with FINTEPLA.

If valvular heart disease or pulmonary arterial hypertension is observed on an echocardiogram, the prescriber must consider the benefits versus the risks of initiating or continuing treatment with FINTEPLA.

FINTEPLA REMS Program (see Boxed Warning): FINTEPLA is available only through a restricted distribution program called the FINTEPLA Risk Evaluation and Mitigation Strategy (REMS) Program. Prescribers must be certified by enrolling in the FINTEPLA REMS. Prescribers must counsel patients receiving FINTEPLA about the risk of valvular heart disease and pulmonary arterial hypertension, how to recognize signs and symptoms of valvular heart disease and pulmonary arterial hypertension, the need for baseline (pretreatment) and periodic cardiac monitoring via echocardiogram during FINTEPLA treatment, and cardiac monitoring after FINTEPLA treatment. Patients must enroll in the FINTEPLA REMS and comply with ongoing monitoring requirements. The pharmacy must be certified by enrolling in the FINTEPLA REMS and must only dispense to patients who are authorized to receive FINTEPLA. Wholesalers and distributors must only distribute to certified pharmacies. Further information is available at www.FinteplaREMS.com or by telephone at 1-877-964-3649.

Decreased Appetite and Decreased Weight: FINTEPLA can cause decreases in appetite and weight. Decreases in weight appear to be dose related. Most patients resumed the expected measured increases in weight by the end of the open-label extension study. Weight should be monitored regularly during treatment with FINTEPLA and dose modifications should be considered if a decrease in weight is observed.

Somnolence, Sedation, and Lethargy: FINTEPLA can cause somnolence, sedation, and lethargy. Other central nervous system (CNS) depressants, including alcohol, could potentiate these effects of FINTEPLA. Prescribers should monitor patients for somnolence and sedation and should advise patients not to drive or operate machinery until they have gained sufficient experience on FINTEPLA.

**Dosage and Administration**

- The maximum daily maintenance dose of FINTEPLA is 0.35 mg/kg twice daily, not to exceed a total daily dose of 26 mg. When FINTEPLA is coadministered with stiripentol plus vigabatrin, the maximum dose of FINTEPLA is limited to 0.25 mg/kg twice daily, not to exceed a total daily dose of 19 mg.
- FINTEPLA is to be administered orally and may be taken with or without food. The starting dose is 0.1 mg/kg twice daily, which can be increased based on clinical response.

**Drug Interactions**

- CYP1A2 and CYP2B6 inducer will decrease fenfluramine plasma concentrations.
- Antidepressants that inhibit serotonin reuptake, including selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs) may potentiate the serotonin effects of FINTEPLA.
- Drugs that impair metabolism of fenfluramine, including, but not limited to, St. John’s Wort, could potentiate the effects of FINTEPLA.
- Drugs that impair metabolism of fenfluramine, including, but not limited to, St. John’s Wort, could potentiate the effects of FINTEPLA.
Fintepla® (fenfluramine) 2.2 mg/mL oral solution

Profound seizure reduction can leave more room for life’s little victories.
Among patients taking Fintepla 0.7 mg/kg/day over 14 weeks:

- 58% of patients had a profound (275%) reduction in convulsive seizures vs 3% in the placebo group (P<.001)
- 50% of patients achieved a seizure-free (0 seizures) interval lasting at least 21 days vs 8 days in the placebo group (P<.001)

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont.)

Fintepla to gauge whether it adversely affects their ability to drive or operate machinery.

Suicidal Behavior and Ideation: Antiepileptic drugs (AEDs) increase the risk of suicidal thoughts or behaviors in patients taking these drugs for any indication. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviors, or any unusual changes in mood or behavior. Anyone considering prescribing Fintepla or any other AED must balance the risk of suicidal thoughts or behaviors with the risks of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviors. Should suicidal thoughts and behaviors emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Withdrawal of Antiepileptic Drugs: As with most AEDs, Fintepla should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus. If withdrawal is needed because of a serious adverse reaction, rapid discontinuation can be considered.

Serotonin Syndrome: Serotonin syndrome, a potentially life-threatening condition, may occur with Fintepla, particularly during concomitant administration of Fintepla with other serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), bupropion, triptans, dietary supplements (eg, St. John’s Wort, tryptophan), drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs], which are contraindicated with Fintepla), dextromethorphan, lithium, tramadol, and antipsychotics with serotonergic agonist activity. Patients should be monitored for the emergence of signs and symptoms of serotonin syndrome, which include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular symptoms (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If serotonin syndrome is suspected, treatment with Fintepla should be stopped immediately and symptomatic treatment should be started.

Increase in Blood Pressure: Fintepla can cause an increase in blood pressure. Significant elevation in blood pressure, including hypertensive crisis, has been reported rarely in adult patients treated with fenfluramine, including patients without a history of hypertension. Monitor blood pressure in patients treated with Fintepla. In clinical trials of up to 3 years in duration, no patient receiving Fintepla developed hypertensive crisis.

Glaucoma: Fenfluramine can cause mydriasis and can precipitate angle closure glaucoma. Consider discontinuing treatment with Fintepla in patients with acute decreases in visual acuity or ocular pain.

ADVERSE REACTIONS

The most common adverse reactions (incidence at least 10% and greater than placebo) were decreased appetite; somnolence, sedation, lethargy; diarrhea; constipation; abnormal echocardiogram; fatigue, malaise, asthenia; ataxia, balance disorder; gait disturbance; blood pressure increased; drooling, salivary hypersecretion; pyrexia; upper respiratory tract infection; vomiting; decreased weight; fall; status epilepticus.

DRUG INTERACTIONS

Strong CYP1A2 and CYP2B6 Inducers: Coadministration with rifampin or a strong CYP1A2 and CYP2B6 inducer will decrease fenfluramine plasma concentrations. Consider an increase in Fintepla dosage when coadministered with rifampin or a strong CYP1A2 and CYP2B6 inducer.

USE IN SPECIFIC POPULATIONS

Administration to patients with moderate or severe renal impairment or to patients with hepatic impairment is not recommended.

Please see Brief Summary of full Prescribing Information, including Boxed Warning, on the following page.
FINTEPLA® (fenfluramine) oral solution, CIV

WARNING: VALVULAR HEART DISEASE and PULMONARY ARTERIAL HYPERTENSION

There is an association between serotoninergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease and pulmonary arterial hypertension.

Echocardiogram assessments are required before, during, and after treatment with FINTEPLA. The benefits versus the risks of initiating or continuing FINTEPLA must be considered, based on echocardiogram findings.

Because of the risks of valvular heart disease and pulmonary arterial hypertension, FINTEPLA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the FINTEPLA REMS.

CONTRAINDICATIONS

FINTEPLA is contraindicated in patients with:
- Hypersensitivity to fenfluramine or any of the excipients in FINTEPLA
- Concomitant use of, or within 14 days of the administration of monamine oxidase inhibitors because of an increased risk of serotonin syndrome

WARNINGS AND PRECAUTIONS

Valvular Heart Disease

Because of the association between serotoninergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease, cardiac monitoring is required prior to starting treatment, during treatment, and after treatment with FINTEPLA concludes. Cardiac monitoring via echocardiogram can identify evidence of valvular heart disease prior to a patient becoming symptomatic, aiding in early detection of this condition. In clinical trials of up to 3 years in duration, no patient receiving FINTEPLA developed valvular heart disease.

Monitoring

Prior to starting treatment, patients must undergo an echocardiogram to evaluate for valvular heart disease.

Echocardiograms should be repeated every 6 months, and once 3-6 months post-treatment with FINTEPLA.

If valvular heart disease is observed on an echocardiogram, the prescriber must consider the benefits versus the risks of initiating or continuing treatment with FINTEPLA.

FINTEPLA is available only through a restricted program under a REMS.

Pulmonary Arterial Hypertension

Because of the association between serotoninergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and pulmonary arterial hypertension, cardiac monitoring is required prior to starting treatment, during treatment, and after treatment with FINTEPLA concludes. Cardiac monitoring via echocardiogram can identify evidence of pulmonary arterial hypertension prior to a patient becoming symptomatic, aiding in early detection of this condition. In clinical trials of up to 3 years in duration, no patient receiving FINTEPLA developed pulmonary arterial hypertension.

Monitoring

Prior to starting treatment, patients must undergo an echocardiogram to evaluate for pulmonary arterial hypertension.

Echocardiograms should be repeated every 6 months, and once 3-6 months post-treatment with FINTEPLA.

If pulmonary arterial hypertension is observed on an echocardiogram, the prescriber must consider the benefits versus the risks of initiating or continuing treatment with FINTEPLA.

FINTEPLA is available only through a restricted program under a REMS.

FINTEPLA REMS Program

FINTEPLA is available only through a restricted distribution program called the FINTEPLA REMS program because of the risk of valvular heart disease and pulmonary arterial hypertension.

Notable requirements of the FINTEPLA REMS Program include:
- Prescribers must be certified by enrolling in the FINTEPLA REMS program.
- Prescribers must counsel patients receiving FINTEPLA about the risk of valvular heart disease and pulmonary arterial hypertension, how to recognize signs and symptoms of valvular heart disease and pulmonary arterial hypertension, the need for baseline (pretreatment) and periodic cardiac monitoring via echocardiogram during FINTEPLA treatment, and cardiac monitoring after FINTEPLA treatment.
- Patients must enroll in the REMS program and comply with ongoing monitoring requirements.
- The pharmacy must be certified by enrolling in the REMS program and must only dispense to patients who are authorized to receive FINTEPLA.
- Wholesalers and distributors must only distribute to certified pharmacies.

Further information is available at www.FinteplaREMS.com or by telephone at 1-877-964-3649.

Decreased Appetite and Decreased Weight

FINTEPLA can cause decreases in appetite and weight. In Study 1 and Study 2 combined, approximately 37% of patients treated with FINTEPLA reported, as an adverse reaction, decreased appetite and approximately 9% reported decreased weight, as compared to 3% and 1%, respectively, of patients on placebo. By the end of the controlled studies, 19% of patients treated with FINTEPLA had a measured decrease in weight of 7% or greater from their baseline weight, compared to 2% of patients on placebo. This measured decrease in weight appeared to be dose-related, with 20% of patients on FINTEPLA 0.7 mg/kg/day, 19% of patients on FINTEPLA 0.4 mg/kg/day in combination with strontiportel, and 13% of patients taking FINTEPLA 0.2 mg/kg/day experiencing at least a 7% decrease in weight from baseline. Most patients resumed the expected measured increases in weight by the end of the open-label extension study. Given the frequency of these adverse reactions, the growth of pediatric patients treated with FINTEPLA should be carefully monitored. Weight should be monitored regularly during treatment with FINTEPLA and dose modifications should be considered if a decrease in weight is observed.

Somnolence, Sedation, and Lethargy

FINTEPLA can cause somnolence, sedation, and lethargy. In Study 1 and Study 2 combined, the incidence of somnolence, sedation, and lethargy was 25% in patients treated with FINTEPLA, compared with 11% of patients on placebo. In general, these effects may diminish with continued treatment.

Other central nervous system (CNS) depressants, including alcohol, could potentiate these effects of FINTEPLA. Prescribers should monitor patients for somnolence and sedation and advise patients not to drive or operate machinery until they have gained sufficient experience on FINTEPLA to gauge whether it adversely affects their ability to drive or operate machinery.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs) increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs that did not include FINTEPLA showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:0.12, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,020 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

### Table 2: Risk of Suicidal Thoughts or Behaviors by Indication for Antiepileptic Drugs in the Pooled Analysis

<table>
<thead>
<tr>
<th>Indication</th>
<th>Placebo Patients with Events per 1000 Patients</th>
<th>Drug Patients with Events per 1000 Patients</th>
<th>Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients</th>
<th>Risk Difference: Additional Drug Patients with Events per 1000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>1.0</td>
<td>3.4</td>
<td>3.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>5.7</td>
<td>8.5</td>
<td>1.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Other</td>
<td>1.0</td>
<td>1.8</td>
<td>1.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Total</td>
<td>2.4</td>
<td>4.3</td>
<td>1.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>

The relative risk for suicidal thoughts or behavior was higher in clinical trials in patients with epilepsy than in clinical trials in patients with psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing FINTEPLA or any other AED must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Withdrawal of Antiepileptic Drugs

As with most AEDs, FINTEPLA should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus. If withdrawal is needed because of a serious adverse reaction, rapid discontinuation can be considered.
Serotonin Syndrome
Serotonin syndrome, a potentially life-threatening condition, may occur with FINTEPLA, particularly with concomitant administration of FINTEPLA with other serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), bupropion, triptans, dietary supplements (e.g., St. John's Wort, tryptophan), drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs], which are contraindicated with FINTEPLA), dextromethorphan, lithium, tramadol, and antipsychotics with serotonergic agonist activity. Patients should be monitored for the emergence of signs and symptoms of serotonin syndrome, which include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular signs (e.g., hyperreflexia, incoordination), and/ or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). If serotonin syndrome is suspected, treatment with FINTEPLA should be stopped immediately and symptomatic treatment should be started.

Increase in Blood Pressure
FINTEPLA can cause an increase in blood pressure. Significant elevation in blood pressure, including hypertensive crisis, has been reported rarely in adult patients treated with fenfluramine, including patients without a history of hypertension. Monitor blood pressure in patients treated with FINTEPLA. In clinical trials of up to 3 years in duration, no patient receiving FINTEPLA developed a hypertensive crisis.

Glaucoma
Fenfluramine can cause mydriasis and can precipitate angle closure glaucoma. Consider discontinuing treatment with FINTEPLA in patients with acute decreases in visual acuity or ocular pain.

ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in labeling:

- Valvular Heart Disease
- Pulmonary Arterial Hypertension
- Decreased Appetite and Decreased Weight
- Somnolence, Sedation, and Lethargy
- Suicidal Behavior and Ideation
- Withdrawal of Antiepileptic Drugs
- Serotonin Syndrome
- Increase in Blood Pressure
- Glaucoma

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 practice.

In controlled and uncontrolled trials in patients with Dravet syndrome, 341 patients were treated with FINTEPLA, including 312 patients treated for more than 6 months, 284 patients treated for more than 1 year, and 138 patients treated for more than 2 years.

In placebo-controlled trials of patients with Dravet syndrome, 122 patients were treated with FINTEPLA. The duration of treatment in these trials was 16 weeks (Study 1) or 17 weeks (Study 2). In Study 1 and Study 2, the mean age was 9 years (range 2 to 19 years) and approximately 46% of patients were female and 74% were White. All patients were receiving at least one other AED.

In Study 1 and Study 2, the rates of discontinuation as a result of any adverse reaction were 13%, 0%, and 7% for patients treated with FINTEPLA 0.7 mg/kg/day, 0.2 mg/kg/day, and 0.4 mg/kg/day in combination with stiripentol, respectively, compared to 6% for patients on placebo. The most frequent adverse reaction leading to discontinuation in the patients treated with any dose of FINTEPLA was somnolence (n=3, 3%).

The most common adverse reactions that occurred in patients treated with FINTEPLA (incidence at least 10% and greater than placebo) were decreased appetite; somnolence, sedation, lethargy; diarrhea; constipation; abnormal echocardiogram; fatigue; malaise; asthenia; ataxia, balance disorder, gait disturbance; blood pressure increased; drooling, salivary hypersecretion; pyrexia; upper respiratory tract infection; vomiting; decreased weight; fall; status epilepticus.

Table 3 lists the adverse reactions that were reported in 5% or more of patients treated with FINTEPLA and at a rate greater than those on placebo during the titration and maintenance phases of Study 1 and Study 2.

| Table 3: Adverse Reactions in 5% or More of Patients Treated with FINTEPLA and Greater Than Placebo in Placebo-Controlled Trials |
|---------------------------------------------------------------|----------------|----------------|----------------|----------------|
|                                                                 | Study 1         | Study 2         | Combined        | Placebo Group |
| Number of Patients (N)                                         | 0.2 mg/kg/day   | 0.7 mg/kg/day   | 0.4 mg/kg/day   |                |
|                                                             | Study 1 %       | Study 2 %       | Combined %      | Placebo %     |
| Decreased appetite                                           | 23              | 38              | 48             | 9             |
| Somnolence, sedation, lethargy                               | 26              | 25              | 23             | 11            |
| Abnormal echocardiogram(1)                                    | 18              | 23              | 9              | 6             |
| Diarrhea                                                      | 31              | 15              | 23             | 6             |
| Constipation                                                  | 3               | 10              | 7              | 0             |
| Fatigue, malaise, asthenia                                    | 10              | 10              | 30             | 5             |
| Ataxia, balance disorder, gait disturbance                    | 10              | 10              | 7              | 1             |
| Abnormal behavior                                            | 0               | 8               | 9              | 0             |
| Blood pressure increased                                      | 13              | 8               | 2              | 0             |
| Drosting, salivary hypersecretion                             | 13              | 8               | 2              | 0             |
| Hypotonia                                                     | 0               | 8               | 0              | 0             |
| Rash                                                          | 8               | 8               | 5              | 4             |
| Blood prolactin increased                                     | 0               | 5               | 0              | 0             |
| Chills                                                        | 0               | 5               | 2              | 0             |
| Decreased activity                                            | 0               | 5               | 0              | 1             |
| Dehydration                                                   | 0               | 5               | 0              | 0             |
| Insomnia                                                      | 0               | 5               | 5              | 2             |
| Pyrexia                                                       | 15              | 5               | 21             | 14            |
| Stereotypy                                                    | 0               | 5               | 0              | 0             |
| Upper respiratory tract infection                             | 21              | 5               | 7              | 10            |
| Vomiting                                                      | 10              | 5               | 5              | 8             |
| Weight decreased                                              | 13              | 5               | 7              | 1             |
| Croup                                                        | 5               | 3               | 0              | 1             |
| Ear infection                                                 | 8               | 3               | 9              | 5             |
| Gastroenteritis                                               | 8               | 3               | 2              | 0             |
| Increased heart rate                                          | 5               | 3               | 0              | 2             |
| Irritability                                                  | 0               | 3               | 9              | 2             |
| Rhinitis                                                      | 8               | 3               | 7              | 2             |
| Tremor                                                       | 3               | 3               | 3              | 9             |
| Urinary incontinence                                          | 5               | 3               | 0              | 0             |
| Decreased blood glucose                                       | 0               | 0               | 9              | 1             |
| Bronchitis                                                    | 3               | 0               | 9              | 1             |
| Cough                                                        | 5               | 0               | 0              | 0             |
| Eczema                                                        | 0               | 5               | 0              | 0             |
| Enuresis                                                      | 5               | 0               | 0              | 0             |
| Fall                                                          | 10              | 0               | 0              | 4             |
| Headache                                                      | 8               | 0               | 0              | 2             |
| Laryngitis                                                    | 0               | 0               | 5              | 0             |
| Nausea                                                       | 5               | 0               | 0              | 0             |
| Status epileptic                                              | 3               | 0               | 12             | 2             |
| Urinary tract infection                                       | 5               | 0               | 5              | 0             |
| Viral infection                                               | 0               | 0               | 5              | 1             |

(1) 0.4 mg/kg/day was not an intermediate dose. Patients on the 0.4 mg/kg/day dose were also taking concomitant stiripentol plus clobazam, which increases exposure of FINTEPLA.

(2) Patients in placebo groups from Studies 1 and 2 were pooled.

(3) Consisted of trace and mild mitral regurgitation, and trace aortic regurgitation, which are considered physiologic.

Echocardiographic Safety Assessments of Valvular Heart Disease and Pulmonary Arterial Hypertension
Valvular heart disease and pulmonary arterial hypertension were evaluated in the placebo-controlled and open-label extension studies via echocardiography for up to 3 years in duration.

No patient developed echocardiographic findings consistent with either valvular heart disease or pulmonary arterial hypertension in the placebo-controlled studies or during the open-label extension study of up to 3 years in duration. In Study 1 and Study 2, 16% of patients taking FINTEPLA compared to 6% of patients taking placebo were reported to have trace mitral regurgitation, and 3% of patients taking FINTEPLA and no patients taking placebo were found to have trace aortic regurgitation. During the open-label extension study, trace mitral regurgitation and trace aortic regurgitation were reported in 14% and 0.4%, respectively, of patients taking FINTEPLA. Trace and mild mitral regurgitation, and trace aortic regurgitation are considered physiologic in the absence of structural valve abnormalities.
Administration of FINTEPLA to patients with hepatic impairment is not recommended. Hepatic Impairment

Administration of FINTEPLA to patients with moderate or severe renal impairment is not recommended. Renal Impairment

Administration of FINTEPLA to patients with hepatic impairment is not recommended.

Hepatic Impairment

Administration of FINTEPLA to patients with moderate or severe renal impairment is not recommended. Renal Impairment

Administration of FINTEPLA to patients with hepatic impairment is not recommended.

DRUG INTERACTIONS

Effect of Other Drugs on FINTEPLA

Stripletol Plus Clobazam

Coadministration of FINTEPLA with stripletol plus clobazam, with or without valproate, increases fenfluramine plasma concentrations and decreases its metabolite, norfenfluramine, because of the inhibition of the metabolism of fenfluramine. If FINTEPLA is coadministered with stripletol plus clobazam, the maximum daily dosage of FINTEPLA is 0.2 mg/kg twice daily (maximum daily dosage of 17 mg).

Strong CYP1A2 and CYP2B6 Inducers

Coadministration with rifampin or strong CYP1A2 and CYP2B6 inducers will decrease fenfluramine plasma concentrations, which may lower the efficacy of FINTEPLA.

Consider an increase in FINTEPLA dosage when coadministered with rifampin or a strong CYP1A2 and CYP2B6 inducer; however, do not exceed the maximum daily dosage.

Effects of Serotonin Receptor Antagonists

Cyproheptadine and potent 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C serotonin receptor antagonists may decrease the efficacy of FINTEPLA. If cyproheptadine or potent 5-HT1A, 5-HT1D, 5-HT2A, or 5-HT2C serotonin receptor antagonists are coadministered with FINTEPLA, patients should be monitored appropriately.

Serotonergic Drugs

Concomitant administration of FINTEPLA and drugs (e.g., SSRIs, SNRIs, TCAs, MAO inhibitors, trazodone, etc.), over-the-counter medications (e.g., dextromethorphan), or herbal supplements (e.g., St. John’s Wort) that increase serotonin may increase the risk of serotonin syndrome. Concomitant use of FINTEPLA with MAOIs is contraindicated. Use FINTEPLA with caution in patients taking other medications that increase serotonin.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), such as FINTEPLA, during pregnancy. Encourage women who are taking FINTEPLA during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling the toll-free number 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org.

Risk Summary

There are no adequate human or animal data on the developmental risks associated with the use of FINTEPLA in pregnant women.

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 risks of major birth defects and miscarriage for the indicated populations are unknown.

Lactation

Risk Summary

There are no data on the presence of fenfluramine or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for FINTEPLA and any potential adverse effects on the breastfed infant from FINTEPLA or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of FINTEPLA for the treatment of seizures associated with Dravet syndrome have been established in patients 2 years of age and older.

Safety and effectiveness in patients less than 2 years of age have not been established.

Juvenile Animal Data

Oral administration of fenfluramine (0, 3.5, or 20 mg/kg/day) to young rats for 10 weeks starting on postnatal day 7 resulted in reduced body weight and neurobehavioral changes (decreased locomotor activity and learning and memory deficits) at all doses tested. Neurobehavioral effects persisted after dosing was discontinued. Bone size was decreased at the mid and high doses; brain size was decreased at the highest dose. Partial or complete recovery was seen for these endpoints. A no‑effect dose for postnatal developmental toxicity was not identified. The lowest dose tested (3.5 mg/kg/day) was associated with plasma fenfluramine exposures (AUC) less than that in humans at the maximum recommended human dose (MRHD of 30 mg/day) and norfenfluramine (metabolite) exposures (AUC) approximately 3 times that in humans at the MRHD.

Geriatric Use

Clinical studies of FINTEPLA for the treatment of Dravet syndrome did not include patients 65 years of age and older to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment

Administration of FINTEPLA to patients with moderate or severe renal impairment is not recommended.

Hepatic Impairment

Administration of FINTEPLA to patients with hepatic impairment is not recommended.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

FINTEPLA contains fenfluramine, a Schedule IV controlled substance.

OVERDOSAGE

Overdose has not been observed in the FINTEPLA clinical trial program. However, overdose of fenfluramine, the active ingredient in FINTEPLA, has been reported at higher doses than those included in the clinical trial program. Some of the cases were fatal. Events reported after overdose include mydriasis, tachycardia, flushing, tremors/twitching/muscle spasms, agitation/restlessness/anxiety, increased muscle tone/tightness/stiffness, respiratory distress or failure, and seizure. Seizure, coma, and cardiorespiratory arrest were reported in most of the fatal overdoses.

There is no available specific antidote to the overdose reactions of FINTEPLA. In the event of overdose, standard medical practice for the management of drug overdose should be used. An adequate airway, oxygenation, and ventilation should be ensured; monitoring of cardiac rhythm and vital sign measurement is recommended. A certified poison control center should be contacted for updated information on the management of overdose with FINTEPLA.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Administration Information

Advise patients who are prescribed FINTEPLA to use the oral dosing syringes provided by the pharmacy. Instruct patients to discard any unused FINTEPLA 3 months after first opening the bottle or if the “discard after” date on the dispensing bottle has passed, whichever is sooner.

Valvular Heart Disease and Pulmonary Arterial Hypertension

Advise patients that cardiac monitoring must be performed using echocardiography to monitor for serious heart valve changes or high blood pressure in the arteries of the lungs.

FINTEPLA REMS Program

FINTEPLA is available only through a restricted program called the FINTEPLA REMS program. Inform the patient of the following notable requirements:

• Patients must enroll in the program and comply with ongoing echocardiogram monitoring requirements.

FINTEPLA is only prescribed by certified health care providers and only dispensed from certified pharmacies participating in the program. Therefore, provide patients with the telephone number and website for information on how to obtain the product.

Decreased Appetite and Decreased Weight

Advise patients that decreased appetite is frequent during treatment with FINTEPLA, which can cause decrease in weight.

Somnolence, Sedation, and Lethargy

Inform patients that FINTEPLA can cause somnolence, sedation, and lethargy. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that FINTEPLA does not affect them adversely (eg, impair judgment, thinking, or motor skills).

Suicidal Thinking and Behavior

Counsel patients, their caregivers, and their families that antiepileptic drugs may increase the risk of suicidal thoughts and behavior and advise them to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Instruct patients, caregivers, and families to report behaviors of concern immediately to healthcare providers.

Withdrawal of Antiepileptic Drugs (AEDs)

Advise patients not to discontinue use of FINTEPLA without consulting with their healthcare provider. FINTEPLA should normally be gradually withdrawn to reduce the potential for increased seizure frequency and status epilepticus.

Serotonin Syndrome

Inform patients about the risk of serotonin syndrome, which can be life-threatening. Advise patients on the signs and symptoms of serotonin syndrome and that certain over-the-counter and herbal supplements can increase this risk.

Increase in Blood Pressure

Inform patients that FINTEPLA can cause an increase in blood pressure.

Glaucma

Inform patients that FINTEPLA can cause mydriasis and can precipitate angle closure glaucoma. Instruct patients to contact their healthcare provider if they have any acute decreases in visual acuity or ocular pain.

Pregnancy Registry

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during FINTEPLA therapy. Encourage women who are taking FINTEPLA to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy.

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**Recent Advances in the Understanding of Insomnia**

**INSOMNIA IS THE COMPLAINT OF DISSATISFACTION** with sleep quantity or quality associated with an inability to fall or stay asleep or early-morning awakening. Considerable changes have occurred in our understanding of insomnia over the past few decades. Whereas it was once thought to be an uncommon malady, we now know that it is highly prevalent in clinical settings; after pain, it represents the second-most commonly expressed clinical complaint. In community settings, an astounding 35% of the adult population experiences insomnia during the course of 1 year, and that half experiences the problem as severe. Literature suggests 20.1% of adults are dissatisfied with their sleep or take medication for sleeping difficulties. Insomnia is also an emerging problem in children and adolescents; an estimated 4% of children complain of insomnia at least 3 times per week over the course of a year.

Although it was once regarded as a benign condition, insomnia is now also known to be associated with a variety of health risks and consequences. Insomniacs suffer from greater functional impairments, cognitive deficits, work-related impairments and absenteeism, social upheaval, and mood impairments than do good sleepers. They also exhibit greater cognitive deficits especially when responding to challenging reaction time tasks. Insomnia also contributes to the development of new cardiovascular and metabolic abnormalities such as hypertension, heart failure, and glucose intolerance.

Difficulty falling asleep, frequent nocturnal awakenings, early-morning awakening, nonrestorative sleep, decreased total sleep, and disturbing dreams are commonly reported by patients with major depression. However, persistent insomnia, even in the absence of current mood or other disorders, confers an increased future risk of the development of depression and other new psychiatric disorders over the course of the ensuing year, a risk that diminishes if the insomnia resolves and after direct management of insomnia. Insomnia also contributes to suicidal ideation and behavior, and direct management of insomnia diminishes suicidal ideation. There may, therefore, exist a bidirectional relationship between insomnia and various psychiatric disorders including depression.

Earlier formulations into the pathophysiology of insomnia were based on the notion that insomnia represented a failure of the normal process of dreaming, leading to anxiety resulting in awakenings. Later formulations focused on cognitive and behavioral principles; insomniacs were theorized to have an exaggerated emotional reaction to everyday stressors, compounded by distorted and negative beliefs about sleep that led to a cycle of catastrophizing apprehension and worry. More recent research has implicated the role of an overly active physiological arousal system, both during sleep and wakefulness. Insomniacs are so aroused that they have a decreased ability to fall asleep during daytime nap tasks, display increased high-frequency beta electroencephalogram power across the entire night, and have an increase in positron emission tomography global glucose metabolic rates during both wakefulness and sleep compared with healthy controls. Insomniacs also exhibit an increase in heart rate and an increase in whole-body metabolic rate.

The current view of insomnia, which supports the possibility of its existence as an autonomous disorder, is reflected in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. The primary insomnia diagnosis that appeared in prior versions is eliminated, in favor of insomnia disorder, and secondary insomnia conditions are eliminated altogether, in favor of insomnia disorder with concurrent specification of clinically comorbid medical and psychiatric conditions.

We now recognize that the complex nature of insomnia necessitates a systematic evaluation prior to proceeding with treatment, as noted in a number of recently published guidelines. The Insomnia Severity Index is a useful clinical tool for identifying insomnia and measuring...
Digital sleep diaries now afford patients the opportunity to display sleep-wake patterns over time and assist in clinical diagnosis. An actigraph, through a device resembling a wristwatch, records movement and ambient light levels and can be useful for the assessment of sleep patterns and the response to behavioral or pharmacological treatments.

Cognitive behavioral therapy for insomnia (CBT-I) remains the gold standard for insomnia treatment, with proven techniques such as sleep hygiene education, stimulus control therapy, relaxation therapies, restriction of time in bed, cognitive therapy, and paradoxical intention. Limitations in availability of CBT-I are now being addressed by the introduction of unguided online and smartphone CBT-I modules and techniques that can be delivered over 4 weeks. Significant advances have also been made in the pharmacological management of insomnia, which had, over the past few decades, relied on older benzodiazepine receptor agonists. More recently, a melatonin receptor agonist, a histamine-1 receptor antagonist, and 2 orexin receptor antagonists have been introduced, and more are being developed. With the increase in the array of available hypnotics, each with identifiable clinical effects, clinicians can now select hypnotic agents based on specific clinical and disease characteristics, such as age, specific insomnia type (initiation vs maintenance insomnia), presence of respiratory comorbidities (chronic obstructive pulmonary disease, sleep apnea), and a history of substance use/abuse.

In conclusion, decades of research confirms that insomnia is a highly prevalent condition with a variety of health risks and clinical consequences. Neurophysiological studies indicate that it is likely a disturbance of central nervous system hyperarousal with far-reaching effects throughout the body. In addition, it is now viewed as an autonomous disorder that is capable of interacting with comorbid disorders in a bidirectional fashion. A plethora of cognitive/behavioral and pharmacological treatments are also available to the clinician to address the specific clinical needs of the patient with insomnia.

For a full list of references, see the article on NeurologyLive.com.
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FDA Advisory Committee Fails to Recommend Aducanumab Approval

The FDA’s Peripheral and Central Nervous System Drugs Advisory Committee voted not to recommend regulatory approval of Biogen’s aducanumab, in one of the most anticipated advisory committee decisions of the year.1

In the final vote, which assessed whether the findings from the EMERGE trial (Study 302; NCT02484547)—in the context of information from studies 301, 302, and 103 and pharmacodynamic data—could serve as primary evidence for the effectiveness of aducanumab in Alzheimer disease, the committee voted 10:0:1 (10, no; 0, yes; 1, uncertain) that the trial did not provide such evidence.

The committee voted 8:1:2 (8, no; 1, yes; 2, uncertain) that the phase 3 EMERGE study in patients with mild Alzheimer disease was enough to demonstrate efficacy. Additionally, the group voted 7:0:4 (7, no; 0, yes; 4, uncertain) that the prior phase 1 study, PRIME (NCT01677572), demonstrated supporting evidence of efficacy. As for the presence of strong evidence of the therapy’s pharmacodynamic effect on Alzheimer disease, the committee voted 0:5:6 (0, no; 5, yes; 6, uncertain).

In the final slide of the statistical review of aducanumab, the committee summarized that “at best, the evidence in this application is from [EMERGE] only and there exists compellingly conflicting phase 3 evidence,” noting that the approval of aducanumab could present challenges for other candidate therapies with regard to noninferiority, as well as issues with recruitment and retention for ongoing trials.

They did acknowledge Biogen for its design of the clinical trials and its inclusion of biomarker-based data, as well as its subsequent effort to get the data on track for approval, calling for more collaboration between sponsors and the FDA in these processes.

“Biogen thanks the many patients and advocates who shared their personal thoughts and experience at today’s Advisory Committee meeting, reflecting the significant unmet need for a treatment for Alzheimer,” said Michel Vounatsos, CEO of Biogen, in a statement. “We appreciated the opportunity to share our data with the Advisory Committee, and we will continue to work with the FDA as it completes its review of our application.”

Aducanumab’s ultimate fate remains in the hands of the FDA, as Biogen’s biologics license application is currently under review with a Prescription Drug User Fee Act target action date of March 7, 2021, if not sooner. Importantly, although the opinions presented in these committee meetings can influence the agency’s final approval decision, the FDA can—and has—approved drug therapies that were not previously recommended during these exercises.

This result adds to the ongoing contentiousness surrounding the interpretation of the data from EMERGE and ENGAGE (NCT02477800). Thomas M. Wisniewski, MD, professor of neurology and director of the Pearl I. Barlow Center for Memory Evaluation and Treatment at NYU Langone Health in New York, who was not affiliated with the studies, told NeurologyLive® that he believes the evidence is clear.

“There were clear cognitive benefits on a number of end point measures, which [is] unprecedented in a phase 3 Alzheimer disease trial, and furthermore, there was a very clear indication of target engagement, as measured by a dose-dependent reduction in amyloid plaques on amyloid PET [positron emission tomography],” he explained. “As well, very significantly, there were reductions in phosphorylated tau in the subset of patients that had cerebrospinal fluid examinations—again, in a dose-dependent manner.”

Wisniewski added that the potential of aducanumab is “game-changing” and that even though the effect size is not necessarily enormous, “it does look like it’s disease modifying and of cognitive benefit.”

In late October, Howard Fillit, MD, founding executive director and chief science officer of the Alzheimer’s Drug Discovery Foundation, who was also not part of the clinical trials, told NeurologyLive® that, in the least, the trials represent progress in the Alzheimer space. “I think the incremental work that aducanumab represents is really a step forward. Will it be the cure? It won’t be a cure. We’re going to need combination therapy; we’re going to have to hit multiple targets, just like other diseases of aging. From the perspective of history, it’s a very exciting time in Alzheimer research,” he said.

Earlier in that week, a perspective piece published in Alzheimer’s & Dementia called for a third and definitive phase 3 trial of aducanumab, suggesting that the proposed efficacy of the therapy based on available data from a pair of phase 3 trials is unclear.1 That article was followed by a response from 2 of the drug’s key investigators, Marwan N. Sabbagh, MD, and Jeffrey L. Cummings, MD, ScD. Ultimately, they explained that the data warrant approval with accompanying phase 4 surveillance, a stance that has been endorsed by the Alzheimer’s Association.

Aducanumab’s journey to the FDA has been full of ups and downs. After a futility analysis published in March 2019 showed that the therapy missed its primary end point—change in the Clinical Dementia Rating Sclae-Sum of Boxes (CDR-SB) score in patients with mild cognitive impairment due to Alzheimer disease and mild Alzheimer dementia—October 2019 brought a change in course with the reports of an additional analysis of the EMERGE data set, which showed statistically significant changes on the CDR-SB score, with P values of .010 or .031 based on cutoff dates.8 Notably, by the 78-week cutoff in EMERGE’s intention-to-treat population, who received high-dose aducanumab, there was a 22% reduction in clinical decline observed. The opportunity-to-complete population reported similar results. As well, a consistent reduction in clinical decline was observed in the secondary end points, measured by the Mini-Mental State Exam (18% vs placebo; P = .05), the Alzheimer’s Disease Assessment Scale–Cognitive Subscale 13 Items (27% vs placebo; P = .01), and the Alzheimer’s Disease Cooperative Study–Activities of Daily Living Inventory Mild Cognitive Impairment Version (40% vs placebo; P = .001). Imaging data suggested that both doses of therapy were associated with a reduction in amyloid plaque deposit burden at both weeks 26 and 78 compared with placebo (P < .001).
The October report included an additional 3 months of data from the subjects who received a high dose of the drug. At the time, Biogen noted that although ENGAGE failed to meet its end points, data from patients in that trial who achieved sufficient exposure to high-dose aducanumab supported the findings from the EMERGE trial.

In January 2019, the FDA gave the go-ahead for a phase 3b redosing clinical trial of aducanumab (NCT04241068) to demonstrate long-term safety and tolerability in a targeted enrollment of 2400 patients from 4 previous clinical trial programs in the aducanumab development program.

JOURNAL ROUNDUP

Laser Ablation Therapy for Drug-Resistant Epilepsy Is Safe, Effective

A new multicenter study investigated 1-year outcomes of minimally invasive surgical treatment with laser interstitial thermal therapy (LITT) and found it to be a safe and effective treatment option for patients with drug-resistant epilepsy (DRE).

At 1-year follow-up, 64.3% (n = 27; 95% CI, 48.0%-78.5%) of patients in the cohort were free of disabling seizures (reaching Engel I on the Surgery Outcome Scale) and more than 95% of patients had worthwhile seizure reduction (Engel I-III). The median length of stay after LITT was 32.7 hours, and head pain at discharge averaged 1.4 (standard deviation, ± 2.1) on a scale of 1 to 10. Seizure worry (P = .0219) and social functioning scores (P = .0175) improved significantly at 1-year follow-up after treatment, as measured by the Quality of Life in Epilepsy questionnaire (QOLIE-31).1

Principal author Patrick Landazuri, MD, director of the Epilepsy Fellowship Program, Department of Neurology, at the University of Kansas School of Medicine in Kansas City, and colleagues stated that “this initial reporting of an ongoing prospective multicenter study presents further data in support of LITT as a surgical treatment for DRE. Our procedural and safety data continue to indicate LITT as a well-tolerated and safe treatment option….The primary success of LITT remains in well-localized lesions/localizations such as mesial temporal lobe epilepsy/mesial temporal sclerosis [MTLE/MTS], cortical dysplasia, and hypothalamic hamartoma.”

The authors of the study, including Jerry J. Shih, MD, director of the Epilepsy Center at UC San Diego Health, examined the 1-year outcomes of patients enrolled in the multicenter, prospective LAANTERN registry (NCT02392078) specifically for epilepsy treatment. They looked at the 60 LITT procedures performed for DRE. Patients with MTLE/MTS comprised 56.7% (n = 34) of the procedures, with the other procedures performed on patients with stereoelectroencephalography target/seizure focus, focal cortical dysplasia, hypothalamic hamartoma, cavernoma, heterotopias, and tuberous sclerosis. There was no statistical difference between Engel I outcome between MTLE/MTS patients and patients with other epileptic etiologies (P = .1642). Two patients (4.8%) had an Engel IV outcome of no meaningful reduction of seizures. Patients who reached Engel I or II outcome were defined as responders. Previous anterior temporal lobectomy to the LITT target was found to be a negative predictor of Engel I or II outcome, comprising 6.5% (95% CI, 10.9%-69.2%) of responders and 36.4% (95% CI, 10.9%-69.2%) of nonresponders (P = .0321).

The median baseline of QOLIE-31 was 51.7 (range, 8.7-77.3) before LITT and increased by 14.1 points to 55.8 (range, −48.9 to 58.1) after 1-year follow-up, with 73.4% (n = 21; 95% CI, 52.8%-87.3%) reporting an improvement of quality of life. This total score change was not statistically significant (P = .2173), but previous work suggests that an 11.8-point difference indicates a clinically meaningful change. Seizure worry and social functioning scores drove the increase in total point scores.

Soon after LITT, 5 procedure-related adverse events (AEs) did occur, 1 classified as serious. Headaches occurred in 2 patients, 1 of whom also experienced nausea and dizziness. Another patient had a 3-mm right convexity subdural hematoma related to LITT. All 3 of these AEs resolved without intervention. A fourth patient had mild aphasia and headache and continued to suffer mild paraphasias at 1-year follow-up. The last patient had 2 LITT procedures after seizures did not initially abate. The second resulted in an intraparenchymal hemorrhage that was immediately treated but resulted in right hemiparesis and expressive aphasia that required rehabilitation. At 1-year follow-up, the fifth patient’s neurological exam returned to baseline.

“Though epilepsy surgery is a highly effective treatment for select patients with drug-resistant epilepsy, it continues to be underutilized, possibly due at least in part to patient and physician concern of surgical risk,” Landazuri said in a statement. “The availability of minimally invasive options for patients is an important step forward, as suggested by our finding that 84% of patients in this study indicated to their physicians a preference for a minimally invasive option for their epilepsy surgery.”

Sodium Oxybate Improves Nocturnal RBD and REM Sleep Without Atonia in Narcolepsy

Sodium oxybate (SO), a first-line treatment of type 1 narcolepsy (NT1), has the ability to improve nocturnal rapid eye movement (REM) sleep behavior disorder (RBD) and REM sleep without atonia (RSWA) in patients with NT1, according to a newly published study.1

The study evaluated 19 children and adolescents with NT1 (mean age, 12.5 [standard deviation, ± 2.7] years; mean disease duration, 3.4 [standard deviation, ± 1.6] years) who underwent 3 months of stable treatment with SO. RSWA, automatically computed by the validated REM sleep atonia index (RAI), was significantly improved (P < .05) in patients who received the drug compared with baseline.

Study author Giuseppe Plazzi, MD, director of the Sleep Laboratory, Department of Neurological Sciences, at the University of Bologna in Italy, and colleagues noted that the treatment “remarkably” reduced complex movements during REM sleep. They wrote that the
improvements in RBD and RSWA point to a direct role of the drug in modulating motor control.

“In our cohort, the significant increase of RAI implies that the decrease of motor episodes during REM sleep cannot be only ascribed to the reduction of the amount of REM sleep and the increase of deep sleep, but reflects a direct effect of SO in improving and stabilizing muscle atonia during REM sleep,” Antelmi et al concluded.

Compared with baseline, children who received the drug improved in clinical complaints and showed a decrease of the Epworth Sleepiness Scale score (14.4 [± 9.01] vs 3.25 [± 4.87]; t = 5.05; P < .0001).

The treatment also had an effect on the different distribution of sleep stages. Compared with baseline, there was a decrease of the percentage of non-REM (NREM) sleep stage 1 (14.2 [± 9.01] vs 3.25 [± 4.87]; t = 4.04; P < .0005) and of REM sleep (23.1 [± 7] vs 13.1 [± 6.45]; t = −6.50; P < .0001), and an increase of NREM sleep stage 3 (11.1 [± 10.13] vs 53.9 [± 17.96]; t = −5.34; P < .0001).

Patients within the study underwent neurological investigations and video-polysomnography (v-PSG) at baseline and after 3 months of stable treatment with SO. To properly rate RBD episodes, v-PSG was independently analyzed by 2 sleep experts. The v-PSG included at least 3 electroencephalography channels (frontal, central, and occipital leads, referred to the contralateral mastoid), bilateral electrooculogram, submentalis and anterior tibialis electromyography, respiratory parameters, and electrocardiogram.

Antelmi and colleagues noted, “This study offers class IV evidence of the positive effect of SO on modulation of muscle atonia during REM sleep in NT1 children, because of the absence of a control group.”

The investigators also noted that future studies are needed to confirm the findings in adults with NT1 and in patients with idiopathic RBD.

In 2002, the original formulation of SO was approved as a central nervous system (CNS) depressant, marketed as Xyrem, to treat symptoms of narcolepsy in adults. The drug was available only through a Risk Evaluation and Mitigation Strategy program mandated by the FDA. Additionally, it was approved with a black box warning because of its ability to potentially cause depression, seizures, coma, or death, especially in combination with other CNS depressants.

In January 2017, the FDA approved the first generic version of SO oral solution, for the treatment of both cataplexy and excessive daytime sleepiness in narcolepsy in adult patients. The treatment’s label was also expanded in October 2018, to include an indication to treat cataplexy or excessive daytime sleepiness in patients 7 and older with narcolepsy.

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@SKriegerMD on investigating benefits of #nabiximols for #MS spasticity @neurology_live: NeurologyLive reached out to @SKriegerMD to learn more about the challenges of getting nabiximols and other #cannabinoids approved in the US versus other countries.

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BARRIERS TO IDENTIFYING NONMOTOR SEIZURES
Jacqueline French, MD, director, Translation Research and Clinical Trials Epilepsy, NYU Grossman School of Medicine, discusses the need to improve education about nonmotor seizures in focal epilepsy.
VIEW VIDEO neurosciencelive.com/identifying-nonmotor-seizures

BRAIN ENERGY RESCUE BY MEDIUM CHAIN TRIGLYCERIDES
Stephen Cunnane, PhD, professor, Research Center on Aging, Universite de Sherbrooke, discusses how a recent study of a ketogenic medium chain triglyceride drink supports the concept of brain energy rescue.
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THE VASCULAR IMPLICATIONS OF ALZHEIMER DISEASE
Costantino Iadecola, MD, Anne Titzell Professor of Neurology, and director and chair, Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, discusses the shortcomings of the current clinical approach to Alzheimer disease and offers insight into how vascular risk factors play a role in its pathology.
LISTEN neurosciencelive.com/podcast-vascular-alzheimers

HOW SOCIAL ISOLATION CAN AFFECT DISEASE SEVERITY
Indu Subramanian, MD, director, VA Southwest Parkinson’s Disease Research, Education, and Clinical Centers, and faculty, UCLA, discusses the implications of a recent study suggesting that loneliness and social isolation can actually be a predictor of disease worsening in Parkinson disease.
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INDICATION

MAYZENT® (siponimod) 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.

IMPORTANT SAFETY INFORMATION

Contraindications
- Patients with a CYP2C9*3/*3 genotype
- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III/IV heart failure
- Presence of Mobitz type II second-degree, third-degree atrioventricular block, or sick sinus syndrome, unless patient has a functioning pacemaker

Infections: MAYZENT may increase risk of infections with some that are serious in nature. Life-threatening and rare fatal infections have occurred.

Before starting MAYZENT, review a recent complete blood count (CBC) (ie, within 6 months or after discontinuation of prior therapy). Delay initiation of treatment in patients with severe active infections until resolved. Employ effective treatments and monitor patients with symptoms of infection while on therapy. Consider discontinuing treatment if patient develops a serious infection.

Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another sphingosine 1-phosphate (S1P) receptor modulator. Rare cases of CM have occurred with MAYZENT. If CM is suspected, MAYZENT should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

No cases of progressive multifocal leukoencephalopathy (PML) were reported in MAYZENT clinical trials; however, they have been observed in patients treated with another sphingosine 1-phosphate (S1P) receptor modulator and other multiple sclerosis (MS) therapies. If PML is suspected, MAYZENT should be discontinued.

Cases of herpes viral infection, including one case of reactivation of varicella zoster virus leading to varicella zoster meningitis, have been reported. Patients without a confirmed history of varicella zoster virus (VZV) or without vaccination should be tested for antibodies before starting MAYZENT. If VZV antibodies are not present or detected, then VZV immunization
Important Safety Information (Cont)

Infections (cont): is recommended and MAYZENT should be initiated 4 weeks after vaccination.

Use of live vaccines should be avoided while taking MAYZENT and for 4 weeks after stopping treatment.

Caution should be used when combining treatment (ie, anti-neoplastic, immune-modulating, or immunosuppressive therapies) due to additive immune system effects.

Macular Edema: In most cases, macular edema occurred within 4 months of therapy. Patients with history of uveitis or diabetes are at an increased risk. Before starting treatment, an ophthalmic evaluation of the fundus, including the macula, is recommended and at any time if there is a change in vision. The use of MAYZENT in patients with macular edema has not been evaluated; the potential risks and benefits to the individual patient should be considered.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
IMPORTANT SAFETY INFORMATION (CONT)

**Bradyarrhythmia and Atrioventricular Conduction Delays:** Prior to initiation of MAYZENT®, an ECG should be obtained to determine if preexisting cardiac conduction abnormalities are present. In all patients, a dose titration is recommended for initiation of MAYZENT treatment to help reduce cardiac effects.

MAYZENT was not studied in patients who had:

- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization
- New York Heart Association Class II-IV heart failure
- Cardiac conduction or rhythm disorders, including complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia, sick sinus syndrome, Mobitz type II second-degree AV-block or higher-grade AV-block (either history or observed at screening), unless patient has a functioning pacemaker
- Significant QT prolongation (QTc greater than 500 msec)
- Arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs

Reinitiation of treatment (initial dose titration, monitoring effects on heart rate and AV conduction [ie, ECG]) should apply if ≥4 consecutive daily doses are missed.

**Respiratory Effects:** MAYZENT may cause a decline in pulmonary function. Spirometric evaluation of respiratory function should be performed during therapy if clinically warranted.

**Liver Injury:** Elevation of transaminases may occur in patients taking MAYZENT. Before starting treatment, obtain liver transaminase and bilirubin levels. Closely monitor patients with severe hepatic impairment. Patients who develop symptoms suggestive of hepatic dysfunction should have liver enzymes checked, and MAYZENT should be discontinued if significant liver injury is confirmed.

**Increased Blood Pressure:** Increase in systolic and diastolic pressure was observed about 1 month after initiation of treatment and persisted with continued treatment. During therapy, blood pressure should be monitored and managed appropriately.

**Fetal Risk:** Based on animal studies, MAYZENT may cause fetal harm. Women of childbearing potential should use effective contraception to avoid pregnancy during and for 10 days after stopping MAYZENT therapy.

**Posterior Reversible Encephalopathy Syndrome (PRES):** Rare cases of PRES have been reported in patients receiving a sphingosine 1-phosphate (SIP) receptor modulator. Such events have not been reported for patients treated with MAYZENT in clinical trials. If patients develop any unexpected neurological or psychiatric symptoms, a prompt evaluation should be considered. If PRES is suspected, MAYZENT should be discontinued.

**Unintended Additive Immunosuppressive Effects From Prior Treatment or After Stopping MAYZENT:** 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.

Initiating treatment with MAYZENT after treatment with alemtuzumab is not recommended. After stopping MAYZENT therapy, siponimod remains in the blood for up to 10 days. Starting other therapies during this interval will result in concomitant exposure to siponimod.

Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping therapy. However, residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3-4 weeks after the last dose. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore, caution should be applied 3-4 weeks after the last dose of MAYZENT.

**Severe Increase in Disability After Stopping MAYZENT:** Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of an S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping MAYZENT treatment, thus patients should be monitored upon discontinuation.

**Most Common Adverse Reactions:** Most common adverse reactions (>10%) are headache, hypertension, and transaminase increases.

Please see additional Important Safety Information on the previous pages and Brief Summary of full prescribing Information on adjacent pages.

**References:**
MAYZENT® (siponimod) tablets, for oral use
Initial U.S. Approval: 2019

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INICATIONS AND USAGE
MAYZENT is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive dis-
ease, in adults.

4 CONTRAINDICATIONS
MAYZENT is contraindicated in patients who have:
- A CYP2C9 *3/*3 genotype [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.5) in the full prescribing information].
- In the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decom-
sensated heart failure requiring hospitalization, or Class III or IV heart failure.
- Presence of Mobitz type II second-degree, third-degree atrioventricular (AV) block, or sick sinus syndrome, unless patient has a functioning pacemaker [see Warnings and Precautions (5.3)].

5 WARNINGS AND PRECAUTIONS
5.1 Infections
Risk of Infections
MAYZENT causes a dose-dependent reduction in peripheral lymphocyte count to 20–30% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues. MAYZENT may therefore increase the risk of infections; some serious in nature [see Clinical Pharmacology (12.2) in the full prescribing information]. Life-threatening and rare fatal infections have occurred in association with MAYZENT.

In Study 1, a 3-year study [see Clinical Studies (14) in the full prescribing information], the overall rate of infec-
tions was comparable between the MAYZENT-treated patients and those on placebo (49.0% vs. 49.1% respectively). However, herpes zoster, herpes infection, bronchitis, sinusitis, upper respira-
tory infection, and fungal skin infection were more frequent in patients treated with MAYZENT in Study 1. In Study 1, serious infections occurred at a rate of 2.9% in MAYZENT-treated patients compared to 2.5% of patients receiving placebo.

Before initiating treatment with MAYZENT, results from a recent complete blood count (i.e., within 6 months or after discontinuation of prior therapy) should be reviewed.

Initiation of treatment with MAYZENT should be delayed in patients with severe active infection until resolution. Because of potential pharmacodynamic effects such as lowering effects on periph-
eral lymphocyte count, may persist for up to 3-4 weeks after discontinuation of MAYZENT, vigil-
ance for infection should be continued throughout this period [see Warnings and Precautions (5.1)].

Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Suspension of treatment with MAYZENT should be considered if a patient develops a serious infection.

Crytococcal Infections
Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with another sphingosine 1-phosphate (S1P) receptor modulator. Rare cases of CM have also occurred with MAYZENT. Physicians should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. MAYZENT treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Herpes Viral Infections
Cases of herpes viral infection, including one case of reactivation of VZV infection leading to vari-
cella zoster meningitis, have been reported in the development program of MAYZENT. In Study 1, the rate of herpetic infections was 4.6% in MAYZENT-treated patients compared to 5.0% of patients receiving placebo. In Study 1, an increase in the rate of herpes zoster infections was reported in 2.5% of MAYZENT-treated patients compared to 0.7% of patients receiving placebo.

Patients without a healthcare professional confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating MAYZENT [see Vaccinations below].

Progressive Multifocal Leuкоencephalopathy
Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

No cases of PML have been reported in MAYZENT-treated patients in the development program; however, PML has been reported in patients treated with a S1P receptor modulator and other multiple sclerosis (MS) therapies and has been associated with some risk factors (e.g., immunocom-

compromised patients, polytherapy with immunosuppressants). Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. MRI findings may be appar-
ent before clinical signs or symptoms. If PML is suspected, treatment with MAYZENT should be suspended until PML has been excluded.

Prior and Concomitant Treatment with Anti-neoplastic, Immune-Modulating, or Immunosuppressive Therapies
Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be coadministered with caution because of the risk of additive immune system effects during such therapy [see Drug Interactions (7.1)].

Vaccinations
Patients without a healthcare professional confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating MAYZENT treatment. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with MAYZENT, following which initiation of treatment with MAYZENT should be postponed for 4 weeks to allow the full effect of vaccination to occur.

The use of live attenuated vaccines should be avoided while patients are taking MAYZENT and for 4 weeks after stopping treatment [see Drug Interactions (7.1)].

Vaccinations may be less effective if administered during MAYZENT treatment. MAYZENT treatment discontinuation 1 week prior to and until 4 weeks after a planned vaccination is recommended.

5.2 Macular Edema
Macular edema was reported in 1.8% of MAYZENT-treated patients compared to 0.2% of patients receiving placebo. The majority of cases occurred within the first four months of therapy.

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

Continuation of MAYZENT therapy in patients with macular edema has not been evaluated. A decision on whether or not MAYZENT 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 diabetes mellitus are at increased risk of macular edema during MAYZENT therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. In the clinical trial experience in adult patients with all doses of MAYZENT, the rate of macular edema was approximately 10% in MS patients with a history of uveitis or diabetes mellitus versus 2% in those without a history of these diseases. In addition to the examination of the fundus, including the macula, prior to treatment, MS patients with dia-
abetes mellitus or a history of uveitis should have regular follow-up examinations.

5.3 Bradyarrhythmia and Atrialventricular Conduction Delays
Since initiation of MAYZENT treatment results in a transient decrease in heart rate and atrioven-
tricular conduction delays, an up-titration scheme should be used to reach the maintenance
dose of MAYZENT [see Dosage and Administration (2.2, 2.3) and Clinical Pharmacology (12.2) in the full prescribing information].

MAYZENT was not studied in patients who had:
- In the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, or
decompensated heart failure requiring hospitalization
- New York Heart Association Class II-IV heart failure
- In the last 6 months, experienced myocardial infarction,
- In patients with a history of second-degree Mobitz type II or higher AV block, sick-sinus syndrome, Mobitz type I second-de-

gine AV block or higher grade AV block (either history or observed at screening),

- Significant QT prolongation (QTc greater than 500 msec)

- Arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs [see Drug Interactions (7.2)]

Reduction in Heart Rate
After the first titration dose of MAYZENT, the heart rate decrease starts within an hour, and the Day 1 decline is maximal at approximately 3-4 hours. With continued up-titration, further heart rate decreases are seen on subsequent days, with maximal decrease from Day 1-baseline reached on Day 5-6. The highest daily post-dose decrease in absolute hourly mean heart rate is observed on Day 1, with the pulse declining on average 5-6 bpm. Post-dose declines on the fol-

owing days are less pronounced. With continued dosing, heart rate starts increasing after Day 6 and reaches placebo levels within 10 days after treatment initiation.

In Study 1, bradycardia occurred in 4.4% of MAYZENT-treated patients compared to 2.9% of patients receiving placebo. Patients who experienced bradycardia were generally asymptomatic. Few patients experienced symptoms, including dizziness or fatigue, and these symptoms resolved within 24 hours without intervention [see Adverse Reactions (6.1)]. Heart rates below 40 bpm were rarely observed.

Atrialventricular Conduction Delays
Initiation of MAYZENT treatment has been associated with transient atrioventricular conduction delays that follow a similar temporal pattern as the observed decrease in heart rate during dose titration. Any new atrioventricular delay (onset 0-24 h postdose) is a relative contraindication to the use of MAYZENT in patients with a history of ventricular conduction delays, atrial fibrillation or flutter, or congenital atrioventricular conduction defects. After the initiation of MAYZENT treatment, the conduction delays typically are transient, asympto-

matic, resolved within 24 hours, rarely required treatment with atropine, and did not require discontinuation of MAYZENT treatment.

If treatment with MAYZENT is considered, advice from a cardiologist should be sought:
- In patients with significant QT prolongation (QTc greater than 500 msec)

- In patients with arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs [see Drug Interactions (7.2)]

- In patients with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension

- In patients with a history of second-degree Mobitz type II or higher AV block, sick-sinus syn-

drome, or sick-sinus heart block [see Contraindications (4)]

Treatment-Initiation Recommendations
- Obtain an ECG in all patients to determine whether preexisting conduction abnormalities are present.

In all patients, a dose titration is recommended for initiation of MAYZENT treatment to help reduce cardiac effects [see Dosage and Administration (2.2, 2.3) in the full prescribing information].

In patients with sinus bradycardia (HR less than 55 bpm), first- or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure with onset > 6 months prior to initiation, ECG testing and first-dose monitoring is recommended [see Dosage and Administration (2.1, 2.4) in the full prescribing information].

Since significant bradycardia may be poorly tolerated in patients with history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or severe untreated sleep apnea, MAYZENT is not recommended in these patients. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy.
5.9 Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Therapies

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 MAYZENT.

Initiating treatment with MAYZENT after treatment with alemtuzumab is not recommended [see Drug Interactions (7.1)].

5.10 Severe Increase in Disability After Stopping MAYZENT

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 MAYZENT treatment. Patients should be observed for a severe increase in disability upon MAYZENT discontinuation and appropriate treatment should be instituted, as required.

5.11 Immune System Effects After Stopping MAYZENT

After stopping MAYZENT therapy, siponimod remains in the blood for up to 10 days. Starting other therapies during this interval will result in concomitant exposure to siponimod.

Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping therapy [see Clinical Pharmacology (12.2) in the full prescribing information]. However, residual pharmacodynamics effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3-4 weeks after the last dose. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore caution should be applied 3-4 weeks after the last dose of MAYZENT [see Drug Interactions (7.1)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Infections [see Warnings and Precautions (5.1)]
- Macular Edema [see Warnings and Precautions (5.2)]
- Bradycardia and Antiarrhythmic (AV) Conduction Delays [see Warnings and Precautions (5.3)]
- Respiratory Effects [see Warnings and Precautions (5.4)]
- Liver Injury [see Warnings and Precautions (5.5)]
- Increased Blood Pressure [see Warnings and Precautions (5.6)]
- Fetal Risk [see Warnings and Precautions (5.7)]
- Posterior Reversible Encephalopathy Syndrome [see Warnings and Precautions (5.8)]
- Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Therapies [see Warnings and Precautions (5.9)]
- Severe Increase in Disability After Stopping MAYZENT [see Warnings and Precautions (5.10)]
- Immune System Effects After Stopping MAYZENT [see Warnings and Precautions (5.11)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions 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 practice.

A total of 1737 MS patients have received MAYZENT at doses of at least 2 mg daily. These patients were included in Study 1 [see Clinical Studies (14) in the full prescribing information] and in a Phase 2 placebo-controlled study in patients with MS. In Study 1, 67% of MAYZENT-treated patients completed the double-blind part of the study, compared to 59.0% of patients receiving placebo. Adverse events led to discontinuation of treatment in 8.5% of MAYZENT-treated patients, compared to 5.1% of patients receiving placebo. The most common adverse reactions (incidence at least 10%) in MAYZENT-treated patients in Study 1 were headache, hypertension, and transaminase increases.

Table 3 lists adverse reactions that occurred in at least 5% of MAYZENT-treated patients and at a rate at least 1% higher than in patients receiving placebo.

Table 3 Adverse Reactions Reported in Study 1 (Occurring in at Least 5% of MAYZENT-Treated Patients and at a Rate at Least 1% Higher Than in Patients Receiving Placebo)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>MAYZENT 2 mg (N = 1099)</th>
<th>Placebo (N = 546)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Transaminase increased</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Falls</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Terms were combined as follows:
- headache, tension headache, sinus headache, cervicogenic headache, drug withdrawal headache, and procedural headache.
- hypertension, blood pressure increased, blood pressure systolic increased, essential hypertension, blood pressure diastolic increased.
- lalanine aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, liver function test increased, hepatic function abnormal, liver function test abnormal, transaminases increased.
- edema peripheral, joint swelling, fluid retention, swelling face.
- bradycardia, sinus bradycardia, heart rate decreased.
- pain in extremity and limb discomfort.

The following adverse reactions have occurred in less than 5% of MAYZENT-treated patients but at a rate at least 1% higher than in patients receiving placebo: herpes zoster, lymphopenia, seizure, tremor, macular edema, AV block (1st and 2nd degree), asthenia, and pulmonary function test decreased [see Warnings and Precautions (5.1, 5.2, 5.3, 5.4)].
Seizures
In Study 1, cases of seizures were reported in 1.7% of MAYZENT-treated patients, compared to 0.4% in patients receiving placebo. It is not known whether these events were related to the effects of MS, to MAYZENT, or to a combination of both.

Respiratory Effects
Dose-dependent reductions in forced expiratory volume over 1 second (FEV₁) were observed in patients treated with MAYZENT [see Warnings and Precautions (5.4)].

Vascular Events
Vascular events, including ischemic strokes, pulmonary embolisms, and myocardial infarctions, were reported in 3.5% of MAYZENT-treated patients compared to 2.6% of patients receiving placebo. Some of these events were fatal. Physicians and patients should remain alert for the development of vascular events throughout treatment, even in the absence of previous vascular symptoms. Patients should be informed about the symptoms of cardiac or cerebral ischemia caused by vascular events and the steps to take if they occur.

Malignancies
Malignancies such as malignant melanoma in situ and seminoma were reported in MAYZENT-treated patients in Study 1. An increased risk of cutaneous malignancies has been reported in association with another S1P modulator.

7 DRUG INTERACTIONS
7.1 Anti-Neoplastic, Immune-Modulating, or Immunosuppressive Therapies
MAYZENT has not been studied in combination with anti-neoplastic, immune-modulating, or immunosuppressive therapies. Caution should be used during concomitant administration because of the risk of additive immune effects during such therapy and in the weeks following administration [see Warnings and Precautions (5.1)].

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered in order to avoid unintended immunosuppressive effects. [see Warnings and Precautions (5.9)].

Because of the characteristics and duration of alemtuzumab immune suppressive effects, initiating treatment with MAYZENT after alemtuzumab is not recommended.

MAYZENT can generally be started immediately after discontinuation of beta interferon or glatiramer acetate.

7.2 Anti-Arhythmic Drugs, QT Prolonging Drugs, Drugs That May Decrease Heart Rate
MAYZENT has not been studied in patients taking QT prolonging drugs.
Class Ia (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) anti-arrhythmic drugs have been associated with cases of Torsades de Pointes in patients with bradycardia. If treatment with MAYZENT is considered, advice from a cardiologist should be sought.

Because of the potential additive effects on heart rate, treatment with MAYZENT should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arhythymogenic properties, heart rate lowering calcium channel blockers (e.g., verapamil, diltiazem), or other drugs that may decrease heart rate (e.g., ivabradine, digoxin) [see Warnings and Precautions (5.3) and Drug Interactions (7.3)].

If treatment with MAYZENT is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering drugs or appropriate monitoring for treatment initiation.

7.3 Beta-Blockers
Caution should be applied when MAYZENT is initiated in patients receiving treatment with a beta-blocker because of the additive effects on lowering heart rate; temporary interruption of the beta-blocker treatment may be needed prior to initiation of MAYZENT [see Warnings and Precautions (5.3)].
Beta-blocker treatment can be initiated in patients receiving stable doses of MAYZENT [see Clinical Pharmacology (12.2) in the full prescribing information].

7.4 Vaccination
During and for up to one month after discontinuation of treatment with MAYZENT, vaccinations may be less effective; therefore MAYZENT treatment should be paused 1 week prior and for 4 weeks after vaccination [see Warnings and Precautions (5.1)].

The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during MAYZENT treatment and for up to 4 weeks after discontinuation of treatment with MAYZENT [see Warnings and Precautions (5.1)].

7.5 CYPC29 and CYPA344 Inhibitors
Because of a significant increase in exposure to siponimod, concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and moderate or strong CYP344 inhibition is not recommended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP344 dual inhibitor (e.g., fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate - moderate or strong CYP344 inhibitor.

Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inhibitors.

7.6 CYPC29 and CYP344 Inducers
Because of a significant decrease in siponimod exposure, concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and strong CYP344 induction is not recommended for all patients. This concomitant drug regimen can consist of moderate CYP2C9/strong CYP344 dual inducer (e.g., rifampin or carbamazepine) or a moderate CYP2C9 inducer in combination with a separate strong CYP344 inducer.

Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inducers.

Concomitant use of MAYZENT and moderate (e.g., modafinil, efavirenz) or strong CYP344 inducers is not recommended for patients with CYP2C9*1/3 and *2/3 genotype [see Clinical Pharmacology (12.3) in the full prescribing information].

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate data on the developmental risk associated with the use of MAYZENT in pregnant women. Based on animal data and its mechanism of action, MAYZENT can cause fetal harm when administered to a pregnant woman [see Data]. Reproductive and developmental studies in pregnant rats and rabbits have demonstrated MAYZENT-induced embryotoxicity and fetotoxicity in rats and rabbits and increased mortality in rats. Increased incidences of postnatal weight loss and fetal abnormalities (external, urogenital and skeletal) in rat and of embryo-fetal deaths, abortions and fetal variations (skeletal and visceral) in rabbit were observed following prenatal exposure to siponimod starting at a dose 2 times the exposure in humans at the highest recommended dose of 2 mg/day.

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data
Animal Data
When siponimod (0, 1, 5, or 40 mg/kg) was orally administered to pregnant rats during the period of organogenesis, post implantation loss and fetal malformations (visceral and skeletal) were increased at the lowest dose tested, the only dose with fetuses available for evaluation.

A no-effect dose for adverse effects on embryo-fetal development in rats was not identified. Plasma exposure AUC at the lowest dose tested was approximately 18 times that in humans at the recommended human dose (RHD) of 2 mg/day.

When siponimod (0, 0.1, 1, or 5 mg/kg) was orally administered to pregnant rabbits during the period of organogenesis, embryolethality and increased incidences of fetal skeletal variations were observed at all but the lowest dose tested. Plasma exposure (AUC) at the no-effect dose (0.1 mg/kg) for adverse effects on embryo-fetal development in rabbits is less than that in humans at the RHD.

When siponimod (0, 0.05, 0.15, or 0.5 mg/kg) was orally administered to female rats throughout pregnancy and lactation, increased mortality, decreased body weight, and delayed sexual maturatiion were observed in the offspring at all but the lowest dose tested. An increase in malformations was observed at all doses. A no-effect dose for adverse effects on pre- and postnatal development in rats was not identified. The lowest dose tested (0.05 mg/kg) is less than the RHD, on a mg/m² basis.

8.2 Lactation
Risk Summary
There are no data on the presence of siponimod in human milk, the effects of MAYZENT on the breastfed infant, or the effects of the drug on milk production. A study in lactating rats has shown excretion of siponimod and/or its metabolites in milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for MAYZENT and any potential adverse effects on the breastfed infant from MAYZENT or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential
Contraception
Females
Before initiation of MAYZENT treatment, women of childbearing potential should be counselled on the potential for a serious risk to the fetus and the need for effective contraception during treatment with MAYZENT [see Use in Specific Populations (8.1)]. Since it takes approximately 10 days to eliminate the compound from the body after stopping treatment, the potential risk to the fetus may persist and women should use effective contraception during this period [see Warnings and Precautions (5.7)].

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use
Clinical studies of MAYZENT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 CYPC29 Genotype
Before initiation of treatment with MAYZENT, test patients to determine CYPC29 genotype. MAYZENT is contraindicated in patients homoygous for CYPC29*3 (i.e., CYPC29*3/*3 genotype), which is approximately 0.4%-0.5% of Caucasians and less in others, because of substantially elevated siponimod plasma levels. MAYZENT dosage adjustment is recommended in patients with CYPC29*1/3 or *2/*3 genotype because of an increase in exposure to siponimod [see Dosage and Administration (2.3) and Clinical Pharmacology (12.5) in the full prescribing information].

10 OVERDOSAGE
In patients with overdosage of MAYZENT, it is important to observe for signs and symptoms of bradycardia, which may include overnight monitoring. Regular measurements of pulse rate and blood pressure are required, and ECGs should be performed [see Warnings and Precautions (5.3, 5.6) and Clinical Pharmacology (12.2) in the full prescribing information].

There is no specific antidote to siponimod available. Neither dialysis nor plasma exchange would result in meaningful removal of siponimod from the body. The decrease in heart rate induced by MAYZENT can be reversed by atropine or isoprorenaline.

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T2019-45
AS A YEAR OF UNCHECKED SURGES of coronavirus disease 2019 (COVID-19) infection comes to a close, sleep deprivation among health care professionals (HCPs) has become a major concern. Are they functioning well enough at work? Are they showing other signs of stress outside the hospital? Several reviews and surveys have attempted to evaluate and quantify the effects of these unrelenting stressors on the mental and physical health of HCPs treating patients with COVID-19.1,2

A Problem of Unprecedented Magnitude
The impact of the pandemic and subsequent lockdowns on sleep has been universal, according to Michael Grandner, PhD, MTR, CBSM, FAASM, director of the Sleep and Health Research Program and the Behavioral Sleep Medicine Clinic at the University of Arizona College of Medicine in Tucson. In an interview with NeurologyLive®, he said, “There is not 1 person anywhere whose sleep has not been affected at all by the pandemic. It’s a foundation of our biology. Paradoxically, everyone’s sleep is affected differently.”

Lack of sleep among HCPs is now a critical problem, as they struggle to cope with the personal aspects of COVID-19 while treating those who become sick. A meta-analysis of 53 studies reported a pooled prevalence of poor sleep quality in up to 61% of nurses in general, whereas a 2020 survey in China showed that more than one-third of all medical staff there experienced symptoms of insomnia associated with the COVID-19 pandemic.2

“Health care workers in particular have had to work long hours with limited resources and in close proximity to COVID-19 patients during the pandemic,” William D. Killgore, PhD, director of the Social, Cognitive, and Affective Neuroscience (SCAN) Lab in the Department of Psychiatry at the University of Arizona, told NeurologyLive®. The SCAN Lab uses advanced technologies to map neurological processes and responses. “As the hospitalization rates continue to surge again, many health care workers are experiencing high levels of stress, anxiety, depression, burnout, and insomnia,” he said.

Sleep Domains Affected
Sleep parameters affected by the pandemic include sleep latency, duration, and efficiency.3 Some studies suggest that insomnia, or difficulty falling asleep or remaining asleep, is reported by more than half of health care workers who work with patients with COVID-19, Killgore said. “Many health care workers are showing signs of posttraumatic stress, which is often associated with nightmares and disturbed sleep. Unfortunately, sleep is important for the ability to process through emotional experiences, so the sleep disruption due to anxiety, long hours, and stress can lead to a vicious circle that maintains sleep problems and the emotional effects of traumatic experiences.”

Mechanisms of Sleep Deprivation in HCPs
HCPs on the front lines experience greater sleep deprivation as a result of increased sleep restriction from extended work schedules, coupled with various insomnias once they return home. Jessica Dietch, PhD, of the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine in California,
explained that prior to the pandemic, shift work, particularly that involving rotating shifts, was associated with worse sleep across the domains (latency, duration, and efficiency), which were exacerbated with the changing shift demands that occurred once COVID-19 hot spots were apparent.

Additional stressors have included extreme variability in sleep duration along with increased work and family demands, each of which may limit sleep opportunities for HCPs by restricting the average amount of sleep to less than needed.

“Decreased sleep duration, particularly that occurring over multiple days or weeks in a row, can lead to the accumulation of sleep debt,” Dietch told NeurologyLive®.

“Additionally, we know that increases in stressors, which abound for HCPs during the COVID-19 pandemic, can precipitate new insomnia, such as difficulty falling or staying asleep, or exacerbate existing insomnia,” she said.

“Insomnia occurs when there is a decreased ability to detach at night,” Grandner added. This causes sleep to become more fragmented and more shallow, although he noted that in laboratory studies, impairments after a night or 2 of sleep deprivation tend to be less than expected. “Impairments accumulate after a few days or nights of sleep deprivation,” he explained. “Your body will entrain arousal when you’re up night after night, leading to a pattern of chronic insomnia.”

The neurologic impact after loss of sleep over multiple nights is significant. According to Killgore, lack of sleep leads to a reduction of metabolic activity in regions of the brain that are critical for attention, decision-making, and emotional regulation. “Sleep loss has been associated with reduced functional connectivity, ie, communication, between the emotional regions of the brain and the regions that normally regulate those areas, potentially leading to an increased tendency to view experiences from an emotionally skewed, usually negative, perspective,” he said.

Altered Cognition
Sleep deficits begin to lead to pronounced alterations of cognition, Killgore said, with potentially serious consequences. “When a person is lacking restorative sleep, they build up a biological ‘pressure’ to fall asleep, which eventually starts to intrude upon their waking performance in the form of brief attentional lapses. These are momentary glitches, often less than a second in duration, in ongoing cognitive processing where mental activity just seems to stop for a moment. The problem is that these lapses are uncontrollable and occur without warning,” he said, while driving or working, for instance. Consequently, these lapses can be life-threatening.

The most significant impacts on job performance show up not as much in routine, repetitive tasks, according to Grandner, but “when someone has to make a novel judgment call, like when driving home and the light changes or an animal darts into the road.” Such loss of judgment or decision-making abilities resulting from cognitive slowing, in which processing critical information and solving problems take longer, represents potentially the most catastrophic effect of continued sleep loss. Killgore explained that “a sleep-deprived health care provider may not see a simple solution to a simple problem that just takes a different perspective. It also affects judgment and willingness to take risks and how they make moral decisions. So a health care worker who is lacking sleep may make very different life-or-death decisions than they would if they were well rested.”

Disordered Emotional Processing
A tired baby is a cranky baby, and the same is true for adults, although at work, they may try to hide it. Sleep deprivation alters mood and emotional processing as well as alertness. Without sufficient sleep, individuals are prone to emotional and physical burnout, and normally manageable tasks can easily become overwhelming.

Killgore and his colleagues also found that lack of sleep leads to an increase in implicit biases, such as those against individuals of different races or ethnicities. “In our study, when sleep was restricted to 4 hours per night for 3 weeks, implicit biases against Arab Muslims were high, but when the same people got 8 hours of sleep a night for 3 weeks, these biases against others completely disappeared,” he said.

Loneliness is a unique and damaging effect of the ongoing pandemic among HCPs, who are away from their families for longer-than-usual periods and who often have to avoid close contact with those they love because of heightened exposure to the virus at work. “Our data show that as the pandemic has raged on, the levels of loneliness and lack of social support among those under lockdown restrictions have been much worse than those in open communities. We have found that those under lockdown report greater loneliness, depression, anxiety, alcohol abuse, and suicidal thinking than those not under restrictions,” Killgore reported. Lack of sleep has been associated with poor memory and difficulty with attention and concentration. Although causality has not been demonstrated conclusively, nearly every major
psychiatric disorder is associated with sleep problems, he said.

Killgore noted that some studies have suggested that the emotional toll of the pandemic has been greater on women than men in terms of anxiety and depression. “Health care workers who do shift work—ie, working at times that are biologically out of alignment with their normal day-night rhythm—also seem to be at greater risk for insomnia and other psychological problems during the pandemic,” he added.

**Associated Health Risks**

Long-term sleep restriction can have many adverse health effects, Killgore explained. “Most notably, long-term insufficient sleep is associated with increased metabolic disturbances, weight gain, obesity, hypertension, diabetes, and greater risk of heart attacks and stroke, as well as weakened immune function,” he said. Not surprisingly, continued sleep deprivation also presents a higher risk of acquiring COVID-19. “There’s also a potential indirect pathway, in that poor sleep can exacerbate conditions that may be associated with increased risk of infection or complications from COVID-19, like cardiovascular disease,” Dietch said. “Good sleep health is important to support physical and mental health broadly during the COVID-19 pandemic, although it can be hard to come by for HCPs.”

“Lack of sleep leads to worse mood in healthy people, and sleep is critical for processing through emotions and gaining perspective, so there is strong evidence to suggest that chronic sleep restriction can contribute to greater risk for mental health problems,” Killgore suggested. “Our own research has shown that getting more and better quality sleep is associated with greater resilience during the COVID-19 pandemic.”

**Recognizing When Tired Becomes Too Tired**

Killgore pointed out that a sleep-deprived individual who is normally very wise and judicious will not realize when they are sleepy and are making mistakes. Many individuals with chronic sleep problems can get extremely tired and may even fall asleep frequently throughout the day without knowing. He suggested that it is important to take any errors in performance, even minor ones, as serious indicators of impairment. “The best option is to simply follow the science and assume that if you are sleep restricted, you are probably impaired without knowing it,” he said. “Most people will start to show performance deficits after they have been awake longer than 18 hours straight. Performance declines rapidly overnight from about 11 PM to about 8 AM the following morning.”

He suggested that individuals probably show impairment if they are awake at a time when they would normally be sleeping. Chronic sleep restriction down to even 6 hours a night for 2 weeks is nearly equally as impairing as a single night without any sleep, he said, encouraging HCPs to “take it seriously if [they] are dozing off or making simple mistakes at times when [they] should be awake and alert. These are clear signs that [they] are not getting enough sleep.”

Grandner noted that some studies have suggested that the one of the best clues to impairment is the feeling that you’re starting to adjust to the stress” or the recognition of a heightened emotional status—feeling unusually annoyed, sad, or anxious, for instance. “Feeling indecisive or defensive about decisions [is another sign] that you may be sleep impaired,” he added.

“Unfortunately,” Killgore stated, “there is no substitute for sleep. Sleep is an absolute need, and the body will start grabbing it whenever it can, even at the most inopportune moments, if you are not getting enough. The solution isn’t to swing the pendulum in the other direction—it’s to find balance,” Grandner counseled. He suggested that one of the most important things to do after work is to try to disengage from the day.

**Caffeine as a Solution**

When sleepiness sets in, individuals can employ a few strategies to remain more alert in the short term, at least until they can catch up on sleep. All the experts agreed that in the short term, caffeine can be very helpful to maintain alertness but that individuals should use it judiciously, as it remains in the body and can cause sleeplessness even 6 to 12 hours after ingestion. “Although caffeine is very effective at sustaining immediate alertness and vigilance performance, it often produces no measurable improvements in judgment and decision-making quality,” Killgore said.

Grandner agreed, adding that “stimulants, including caffeine, all improve fatigue, reaction time, and alertness but do not rescue decision-making. People just make bad decisions faster,” he said.

**Maintaining Alertness on the Job**

The experts recommended a number of strategies for improving performance and/or wakefulness while at work:

- Take a short walk and seek bright light to promote alertness.
- Consume caffeine early in a shift and cut it off at least 6 to 8 hours before bedtime.
- Eat a snack rather than a large meal during a shift to help promote alertness.
- Schedule small naps in the middle of the day to keep balanced (no more than 15-30 minutes for optimum alertness).

<table>
<thead>
<tr>
<th>TABLE. Getting Good Sleep When the Opportunity Arises</th>
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<tr>
<td>• Keep as regular a schedule as possible (especially wake time) and seek bright light as soon as possible after waking up.</td>
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<tr>
<td>• After working a night shift, try not to sleep right away. Rather, take some time to unwind first.</td>
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<tr>
<td>• Avoid stimulating activities on bright screens before bedtime.</td>
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<td>• Bank sleep if there are upcoming sleep restrictions.</td>
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For a full list of references, see the article on NeurologyLive.com.
Updates in Approaches to Acute Migraine Care

In a NeurologyLive® Peer Exchange, a panel of migraine specialists discussed the novel therapies in development and those entering the market for the treatment of acute migraine.

By Matt Hoffman

EXPECTATIONS FOR ACUTE MIGRAINE treatment are increasing due to the recent uptick in both approved and investigational therapies. With more confidence in the ability to effectively treat acute migraine has come an opportunity to reevaluate how success is measured, with more focus on patient-centered outcomes.

Although conversations in this space have been dominated by the progress and success of the calcitonin gene-related peptide (CGRP)–targeted monoclonal antibodies and the small-molecule gepants, more novel therapies are making their way toward regulatory evaluation. As such, headache and migraine specialists are proceeding with enthusiasm, with the hope of maintaining a reflective approach to gain insights into the possibilities of these new therapies.

In a recent NeurologyLive® Peer Exchange, “Advances in the Management of Acute Treatment of Migraine,” a panel of experts led by Peter J. Goadsby, MD, PhD, DSc, professor of neurology at the University of California, Los Angeles, Goldberg Migraine Program, discussed the mechanisms of action, efficacy, and safety of therapies in the acute migraine treatment armamentarium.

Ditans: 5-HT1F Agonists

In October 2019, the United States Food and Drug Administration (FDA) approved the first member of the ditan class, lasmiditan (Revyow; Eli Lilly), an oral, central nervous system (CNS)–penetrating agent that selectively targets the 5-HT1F receptor. This is in contrast with the triptan class, which targets the serotonin 5-HT1B/1D receptors, though Goadsby noted that some agents, such as naratriptan and sumatriptan, act on the 5-HT1D receptor.

Triptans, which have been available since the early 1990s, can be challenging to use, as they bind to 5-HT1B and blood vessels, causing vasoconstriction. Jelena Pavlovic, MD, PhD, associate professor of neurology at the Albert...
Gepants: CGRP Receptor Antagonists

Cooper and Goadsby then turned to the small-molecule CGRP receptor antagonists, focusing on the 2 approved agents, rimegepant (Nurtec ODT; Biohaven) and ubrogepant (Ubrelvy; AbbVie). Cooper described the mechanistic qualities of these therapies, which work mostly in the periphery, blocking the inflammatory signal coming from the pain-sensitive nerves. Both drugs also suppress inflammation of the meninges.

Additionally, these therapies focus on receptors missed by triptans, in similar fashion to the ditans, making them promising treatments for those who cannot be prescribed triptans or do not derive benefit, which Paul G. Mathew, MD, assistant professor of neurology at Brigham and Women’s Hospital and Harvard Medical School, noted earlier in the discussion.

“What’s also cool about these is that they tend to work relatively quickly,” Cooper said. “Most remarkable from my perspective is their almost complete lack of adverse effects. When you compare the gepants class medicines with the triptan adverse effects, it’s quite phenomenal. Nausea seems to be a reported adverse effect in the clinical trials. I’ve had 1 or 2 people with some pretty severe nausea from it, but as a whole, it’s really well tolerated.”

As for dosing, rimegepant has a set dose of 75 mg while ubrogepant is available in a small range of doses. Pavlovic noted that rimegepant, which comes as an orally disintegrating tablet, provides an appealing ease of administration. Due to the tolerability of these therapies, Cooper noted that he begins dosing at the upper end of the dose range, aiming for the highest efficacy. In comparison, as Pavlovic noted, lasmiditan dosing often requires a “go low, start slow” approach.

“I start at 50 mg in patients who feel relief and may have a lower adverse-effect profile. If they can’t achieve pain freedom completely, then because there is an additive effect to a higher dose, I will increase the dose at that point,” she explained.

Mathew concurred, noting that if a patient easily tolerates 50-mg lasmiditan, he’ll suggest they take a double dose before prescribing 100 mg. “I will do the same thing with ubrogepant, with the instructions that if they tolerate the 50 mg just fine and find it partially effective, try taking 2 of them, then let my office know, and I’ll call in a refill for the 100 mg of that medication as well,” he said.

Intranasal Dihydroergotamine

In addition to the ditans and gepants, there has recently been an attempt to reformulate dihydroergotamine (DHE), a therapy that has been in use since the 1940s. It exists in a number of available formulations, including intravenous, intramuscular, subcutaneous, and inhaled. Mathew noted that DHE causes significant nausea, so it often has to be co-dosed with an antiemetic, giving it a bit of a “bad name.”

“The 2 newer forms of DHE are both intranasal,” he explained. “One of them is a proprietary pump, which squirts the DHE into a
particular part of the nose where it’s able to get absorbed much more consistently. It’s still in liquid formulation. The other is a small vial; you squeeze it, and a powder form of DHE is injected into the nose.”

Mathew noted that these delivery systems are encouraging, in part because of their ability to reach plasma levels lower than the injectable formulations, which helps to avoid some of the associated adverse effects while maintaining a consistent dose.

“Nerve blocks are something you can consider in the office, urgent care, or emergency department,” Mathew said. “But if either of these formulations gets approved, there may potentially be a DHE protocol in which you give the patient a prescription and they can take 1 of these 2 intranasal formulations for a few days. That’s going to be potentially useful for when someone has status migrainosus [and] nothing else is working.”

Dawn C. Buse, PhD, clinical professor of neurology at Albert Einstein College of Medicine, inquired about the potential of DHE as a therapy for women of childbearing age, and if extra education and caution is required in that population.

“Regarding pregnancy, the advice I give many of my patients is that—this is just my view—getting pregnant can take weeks, months, or even years,” Mathew said. “To discontinue someone’s medications because they’re trying to get pregnant can really limit their ability to get pregnant and can lead to a lot of migraines and unnecessary suffering. My advice to these patients is, the minute you become pregnant, call your doctor. We’ll rapidly wean you off everything.”

Buse noted that in the CaMEO study, investigators found that 10% of women with chronic migraine chose not to have children or delayed having children because of concerns associated with their migraine care—either that they would pass on their disease, that they would have to stop their medications, or that their migraine would get worse.

“Anything we can do to treat them as well as possible, keep them comfortable, and allow them to make those lifestyle choices—including reproductive choices, which are core to being human—is important,” she explained. “We also need to think about how, as women age out of a childbearing age and get older, their risk for cardiac events might increase again. We may need to think about a woman who’s maybe been on a triptan for decades, since she was a teen or a young adult. It may be time to reconsider her options as she ages into the postmenopausal age bracket.”

Pavlovic noted that, similar to triptans, registries accounting for the use of the new medications during pregnancy are needed to help build our understanding. “We know that women will inadvertently use them in early pregnancy before awareness that they are pregnant. These medications will be used, and having registries that are active and already started will be very helpful,” she said.

Safety Comparisons

Goadsby then probed the group about their views of the adverse-effect profiles of these agents, as well as compared with those for older medications. Mathew noted that if the patient is taking a CGRP monoclonal antibody, he may be swayed toward prescribing a ditan over a gepant due to its different mechanism of action.

“It’s certainly mechanistically attractive to think that if you have a CGRP blockade, the ditan will come along and block other things that are prejunctionally and presynaptically released,” Goadsby said. “Glutamate is the obvious thing, and perhaps it blocks other peptides. The multi-mechanistic side is useful. Colleagues are also finding that there’s room still to push on the CGRP mechanism, even in people taking monoclonal antibodies. We have a lot of things to learn practically.”

Mathew noted that he offers this simplified description of that process to his patients: The antibody is lowering the overall level of CGRP, so if they happen to experience a migraine, they will have an episodic burst of CGRP, which the gepant can then suppress. He suggested that giving the patient a better understanding of these processes can also improve adherence to treatment, with which Buse agreed.

“These are complex [processes] with many neurotransmitters involved, and when someone knows a bit of what is going on, they’re going to be more comfortable,” Buse said. “They’re going to tolerate any adverse effects that might arise early a bit better, and they’re going to tend to be more adherent. They’re also going to have more comfort with their provider when they’re told in advance what to expect.”

To watch the entire series, visit https://www.neurologylive.com/acute-migraine-PX.
Individual results may vary based on several factors, including severity of disease, initiation of treatment, and duration of therapy.

Victories are personal for the 10,000+ who have been treated with SPINRAZA worldwide.1*

- FOR US PATIENTS TAKING SPINRAZA -

40%

>40% of patients taking SPINRAZA are adults†

3-80

Has treated SMA in patients 3 days‡ to 80 years old1,2†§

90%

>90% of patients who started SPINRAZA remain on treatment†

INDICATION
SPINRAZA is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

IMPORTANT SAFETY INFORMATION
Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. Patients may be at increased risk of bleeding complications.

In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 SPINRAZA-treated patients (16%) with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 sham-controlled patients (14%). Two SPINRAZA-treated patients developed platelet counts <50,000 cells per microliter, with the lowest level of 10,000 cells per microliter recorded on study day 28.

Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. SPINRAZA is present in and excreted by the kidney. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 SPINRAZA-treated patients (58%) had elevated urine protein, compared to 22 of 65 sham-controlled patients (34%).

*Based on commercial patients, early access patients, and clinical trial participants through December 2019.
†Based on commercial patients in the US (including Puerto Rico) through December 2019.
‡Includes clinical trial patients.
§Clinical studies of SPINRAZA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients.
Individual results may vary based on several factors, including severity of disease, initiation of treatment, and duration of therapy.

Learn more at SPINRAZA-hcp.com

IMPORTANT SAFETY INFORMATION (continued)

Laboratory testing and monitoring to assess safety should be conducted. Perform a platelet count, coagulation laboratory testing, and quantitative spot urine protein testing at baseline and prior to each dose of SPINRAZA and as clinically needed.

Severe hyponatremia was reported in an infant treated with SPINRAZA requiring salt supplementation for 14 months.

Cases of rash were reported in patients treated with SPINRAZA.

SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.

The most common adverse reactions (≥20% of SPINRAZA-treated patients and ≥5% more frequently than in control patients) that occurred in the infantile-onset controlled study were lower respiratory infection and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (18%) than in control patients (10%). Because patients in this controlled study were infants, adverse reactions that are verbally reported could not be assessed. The most common adverse reactions that occurred in the later-onset controlled study were pyrexia, headache, vomiting, and back pain. Post-lumbar puncture syndrome has also been observed after the administration of SPINRAZA.

Please see full Prescribing Information at SPINRAZA-hcp.com.

As a courtesy, our full Prescribing Information is also available en Español. For prescribing decisions, please refer to official approved labeling.
**1 INDICATIONS AND USAGE**
SPINRAZA is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

**2 DOSAGE AND ADMINISTRATION**

**2.1 Dosing Information**
SPINRAZA is administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.

**Recommended Dosage**
The recommended dosage is 12 mg (5 mL) per administration.

Initiate SPINRAZA treatment with 4 loading doses. The first three loading doses should be administered at 14-day intervals. The 4th loading dose should be administered 30 days after the 3rd dose. A maintenance dose should be administered once every 4 months thereafter.

**Missed Dose**
If a loading dose is delayed or missed, administer SPINRAZA as soon as possible, with at least 14-days between doses and continue dosing as prescribed. If a maintenance dose is delayed or missed, administer SPINRAZA as soon as possible and continue dosing every 4 months.

**2.2 Important Preparation and Administration Instructions**
SPINRAZA is for intrathecal use only.

Prepare and use SPINRAZA according to the following steps using aseptic technique. Each vial is intended for single dose only.

**Preparation**
- Store SPINRAZA in the carton in a refrigerator until time of use.
- Allow the SPINRAZA vial to warm to room temperature (25°C/77°F) prior to administration. Do not use heat sources.
- Inspect the SPINRAZA vial for particulate matter and discoloration prior to administration. Do not administer SPINRAZA if visible particulates are observed or if the liquid in the vial is discolored. The use of external filters is not required.
- Withdraw 12 mg (5 mL) of SPINRAZA from the single-dose vial into a syringe and discard unused contents of the vial.
- Administer SPINRAZA within 4 hours of removal from vial.

**Administration**
- Consider sedation as indicated by the clinical condition of the patient.
- Consider ultrasound or other imaging techniques to guide intrathecal administration of SPINRAZA, particularly in younger patients.
- Prior to administration, remove 5 mL of cerebrospinal fluid.
- Administer SPINRAZA as an intrathecal bolus injection over 1 to 3 minutes using a spinal anesthesia needle [see Dosage and Administration (2.1)]. Do not administer SPINRAZA in areas of the skin where there are signs of infection or inflammation [see Adverse Reactions (6.3)].

**2.3 Laboratory Testing and Monitoring to Assess Safety**
Conduct the following laboratory tests at baseline and prior to each dose of SPINRAZA and as clinically needed [see Warnings and Precautions (5.1, 5.2)]:
- Platelet count
- Prothrombin time; activated partial thromboplastin time
- Quantitative spot urine protein testing

**3 DOSAGE FORMS AND STRENGTHS**
Injection: 12 mg/5 mL (2.4 mg/mL) nusinersen as a clear and colorless solution in a single-dose vial.

**4 CONTRAINDICATIONS**
None.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Thrombocytopenia and Coagulation Abnormalities**
Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides.

In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 (16%) SPINRAZA-treated patients with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 (14%) sham-controlled patients.

In the sham-controlled study in patients with later-onset SMA (Study 2), two SPINRAZA-treated patients developed platelet counts less than 50,000 cells per microliter, with a lowest level of 10,000 cells per microliter recorded on study day 28.

Because of the risk of thrombocytopenia and coagulation abnormalities from SPINRAZA, patients may be at increased risk of bleeding complications. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.
5.2 Renal Toxicity
Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.

SPINRAZA is present in and excreted by the kidney [see Clinical Pharmacology (12.3)]. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 (58%) of SPINRAZA-treated patients had elevated urine protein, compared to 22 of 65 (34%) sham-controlled patients. Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose of SPINRAZA. For urinary protein concentration greater than 0.2 g/L, consider repeat testing and further evaluation.

6 ADVERSE REACTIONS
The following serious adverse reactions are described in detail in other sections of the labeling:
- Thrombocytopenia and Coagulation Abnormalities [see Warnings and Precautions (5.1)]
- Renal Toxicity [see Warnings and Precautions (5.2)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of SPINRAZA cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

The data described below reflect exposure to SPINRAZA in 260 patients (48% male, 80% Caucasian), including 227 exposed for at least 6 months and 181 exposed for at least 1 year. The safety of SPINRAZA was studied in presymptomatic infants with SMA; pediatric patients (approximately 3 days to 16 years of age at first dose) with symptomatic SMA; infants with symptomatic SMA (Study 1; n=80 for SPINRAZA, n=41 for control); in a sham-controlled trial in children with symptomatic SMA (Study 2; n=64 for SPINRAZA, n=42 for control); in open-label studies in presymptomatic and symptomatic infants (n=40); and in open-label studies in later-onset patients (n=56). In Study 1, 58 patients were exposed for at least 6 months and 28 patients were exposed for at least 12 months. In Study 2, 84 patients were exposed for at least 6 months and 82 patients were exposed for at least 12 months.

Clinical Trial in Infantile-Onset SMA (Study 1)
In Study 1, baseline disease characteristics were largely similar in the SPINRAZA-treated patients and sham-control patients except that SPINRAZA-treated patients at baseline had a higher percentage compared to sham-control patients of paradoxical breathing (35% vs 22%), swallowing or feeding difficulties (51% vs 29%) and requirement for respiratory support (26% vs 15%).

The most common adverse reactions that occurred in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were lower respiratory infection and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (18%) than in control patients (10%). Because patients in Study 1 were infants, adverse reactions that are verbally reported could not be assessed in this study.

Table 1. Adverse Reactions that Occurred in at Least 5% of SPINRAZA Patients and Occurred at Least 5% More Frequently or At Least 2 Times as Frequently Than in Control Patients with Infantile-Onset SMA

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SPINRAZA 12 mg(^1) N=80</th>
<th>Sham-Procedure Control N=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower respiratory infection(^2)</td>
<td>55</td>
<td>37</td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>Teething</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract congestion</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Ear infection</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

\(^1\) Loading doses followed by 12 mg (5 mL) once every 4 months
\(^2\) Includes adenovirus infection, bronchiolitis, bronchitis, bronchitis viral, corona virus infection, influenza, lower respiratory tract infection, lower respiratory tract infection viral, lung infection, parainfluenzae virus infection, pneumonia, pneumonia bacterial, pneumonia influenzal, pneumonia moraxella, pneumonia parainfluenzae viral, pneumonia pneumococcal, pneumonia pseudomonal, pneumonia respiratory syncytial viral, pneumonia viral, and respiratory syncytial virus bronchiolitis
In an open-label clinical study in infants with symptomatic SMA, severe hyponatremia was reported in a patient treated with SPINRAZA requiring salt supplementation for 14 months.

Cases of rash were reported in patients treated with SPINRAZA. One patient, 8 months after starting SPINRAZA treatment, developed painless red macular lesions on the forearm, leg, and foot over an 8-week period. The lesions ulcerated and scabbed over within 4 weeks, and resolved over several months. A second patient developed red macular skin lesions on the cheek and hand ten months after the start of SPINRAZA treatment, which resolved over 3 months. Both cases continued to receive SPINRAZA and had spontaneous resolution of the rash.

SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.

Clinical Trial in Later-Onset SMA (Study 2)
In Study 2, baseline disease characteristics were largely similar in the SPINRAZA-treated patients and sham-control patients except for the proportion of SPINRAZA-treated patients who had ever achieved the ability to stand without support (13% vs 29%) or walk with support (24% vs 33%).

The most common adverse reactions that occurred in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were pyrexia, headache, vomiting, and back pain.

Table 2. Adverse Reactions that Occurred in at Least 5% of SPINRAZA Patients and Occurred at Least 5% More Frequently or At Least 2 Times as Frequently Than in Control Patients with Later-Onset SMA (Study 2)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SPINRAZA 12 mg¹ N=84</th>
<th>Sham-Procedure Control N=42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>43%</td>
<td>36%</td>
</tr>
<tr>
<td>Headache</td>
<td>29%</td>
<td>7%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29%</td>
<td>12%</td>
</tr>
<tr>
<td>Back pain</td>
<td>25%</td>
<td>0%</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Fall</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Respiratory tract congestion</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Seasonal allergy</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

¹ Loading doses followed by 12 mg (5 mL) once every 6 months

Post-lumbar puncture syndrome has also been observed after administration of SPINRAZA.

6.2 Immunogenicity
As with all oligonucleotides, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to nusinersen in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenic response to nusinersen was determined in 249 patients with post-baseline plasma samples evaluated for anti-drug antibodies (ADAs). Sixteen patients (6%) developed treatment-emergent ADAs, of which 3 were transient; 13 were considered to be persistent. Persistent was defined as having one positive test followed by another one more than 100 days after the first positive test. In addition, “persistent” is also defined as having one or more positive samples and no sample more than 100 days after the first positive sample. Transient was defined as having one or more positive results and not confirmed to be persistent. There are insufficient data to evaluate an effect of ADAs on clinical response, adverse events, or the pharmacokinetic profile of nusinersen.
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
There are no adequate data on the developmental risk associated with the use of SPINRAZA in pregnant women. When nusinersen was administered by subcutaneous injection to mice throughout pregnancy and lactation, developmental toxicity (long-term neurobehavioral impairment) was observed at all doses tested (see Data). 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
When nusinersen (0, 3, 10, or 25 mg/kg) was administered subcutaneously to male and female mice every other day prior to and during mating and continuing in females throughout organogenesis, no adverse effects on embryofetal development were observed. Subcutaneous administration of nusinersen (0, 6, 12.6, or 25 mg/kg) to pregnant rabbits every other day throughout organogenesis produced no evidence of embryofetal developmental toxicity.

When nusinersen (1.4, 5.8, or 17.2 mg/kg) was administered to pregnant female mice by subcutaneous injection every other day throughout organogenesis and continuing once every six days throughout the lactation period, adverse neurobehavioral effects (alterations in locomotor activity, learning and memory deficits) were observed when offspring were tested after weaning or as adults. A no-effect level for neurobehavioral impairment was not established.

8.2 Lactation
Risk Summary
There are no data on the presence of nusinersen in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for SPINRAZA and any potential adverse effects on the breastfed infant from SPINRAZA or from the underlying maternal condition.

8.4 Pediatric Use
The safety and effectiveness of SPINRAZA in pediatric patients from newborn to 17 years have been established [see Clinical Studies (14.1)].

Juvenile Animal Toxicity Data
In intrathecal toxicity studies in juvenile monkeys, administration of nusinersen (0, 0.3, 1, or 3 mg/dose for 14 weeks and 0, 0.3, 1, or 4 mg/dose for 53 weeks) resulted in brain histopathology (neuronal vacuolation and necrosis/cellular debris in the hippocampus) at the mid and high doses and acute, transient deficits in lower spinal reflexes at the high dose in each study. In addition, possible neurobehavioral deficits were observed on a learning and memory test at the high dose in the 53-week monkey study. The no-effect dose for neurohistopathology in monkeys (0.3 mg/dose) is approximately equivalent to the human dose when calculated on a yearly basis and corrected for the species difference in CSF volume.

8.5 Geriatric Use
Clinical studies of SPINRAZA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

17 PATIENT COUNSELING INFORMATION

Thrombocytopenia and Coagulation Abnormalities
Inform patients and caregivers that SPINRAZA could increase the risk of bleeding. Inform patients and caregivers of the importance of obtaining blood laboratory testing at baseline and prior to each dose to monitor for signs of increased potential for bleeding. Instruct patients and caregivers to seek medical attention if unexpected bleeding occurs [see Warnings and Precautions (5.1)].

Renal Toxicity
Inform patients and caregivers that SPINRAZA could cause renal toxicity. Inform patients and caregivers of the importance of obtaining urine testing at baseline and prior to each dose to monitor for signs of potential renal toxicity [see Warnings and Precautions (5.2)].
**RGMa Inhibition for Repair and Protection in Multiple Sclerosis**

By Jennifer S. Sun, PhD

**MULTIPLE SCLEROSIS (MS) IS AN** autoimmune-mediated disorder of the central nervous system (CNS). There is currently no single defined cause of MS development, but the neurological impairments characteristic of the disease are thought to result from autoimmune- or inflammation-mediated axonal demyelination that impedes nerve conduction.\(^1\) Drug development for MS has been challenging, in part because a comprehensive treatment should address effects of the disease on both the immune system and CNS. Available treatments, which are largely immunosuppressive, cannot reverse neurological deficits by stimulating remyelination or halting progressive neuronal dysfunction. Thus, concurrent treatment of autoimmune reactions and axonal degeneration has been proposed as a potentially more effective approach to MS therapy.\(^1\)

Repulsive guidance molecule-a (RGMa) is a glycosylphosphatidylinositol-anchored membrane protein that, upon binding its receptor neogenin, inhibits neuronal regeneration and regulates cell death.\(^1-3\) Expression of RGMa is upregulated in the CNS of patients with MS, where RGMa is found in active and chronic lesions, normal-appearing gray and white matter, and meningeal infiltrates.\(^2\) In MS, RGMa enhances activation of CD4-positive T cells by dendritic cells presenting myelin sheath self-antigens, initiating an autoimmune response in the white matter of the brain and spinal cord and resulting in axonal demyelination, neurodegeneration, and progressive paralysis.\(^1,3\) The multiple functions of RGMa in the CNS and immune system offer an opportunity to therapeutically and concurrently block the autoimmune reactions and axonal injury observed in neurodegenerative and neuroinflammatory diseases.

Patients with MS have an urgent need for therapies that can reverse neurologic disability by promoting remyelination.\(^4\) RGMa-specific monoclonal antibody (mAb) treatment (**FIGURE**) promises to surpass the current standard of care for MS, which primarily relies on disease-modifying therapies and symptom management. Anti-RGMa mAbs have been shown to attenuate the severity of animal models of MS, such as experimental autoimmune encephalomyelitis (EAE), by inhibiting T-cell activation in the CNS\(^3,5\) while promoting neuroprotection and neuroregeneration.\(^1,2,6\) Along with decreased expression of RGMa in the spinal cord, EAE mouse

![**FIGURE.** RGMa-Specific Monoclonal Antibody Model](image-url)

RGMa-neogenin signaling mediates experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis. Blocking RGMa activity with a neutralizing antibody diminishes immune responses in both the peripheral and central nervous systems. APC, antigen-presenting cell; BBB, blood-brain barrier; EAE, experimental autoimmune encephalomyelitis; RGM, repulsive guidance molecule.

survival was prolonged, accompanied by suppressed secondary progression of disease. In a rat model of spinal cord injury, the beneficial effects of anti-RGMa mAb administration were observed over a period of up to 24 hours post injury. These benefits included reduced tissue degeneration and promotion of neuronal sparing, axonal plasticity, and functional recovery.

Elezanumab (ABT-555; AbbVie) is a fully humanized anti-RGMa mAb that has demonstrated promotion of axonal regeneration, neuroprotection, remyelination, and immune modulation in MS-relevant preclinical models. A phase 1, double-blind, placebo-controlled, randomized, escalating 4-dose 29-week study was completed in April 2018 (NCT02601885). The study examined 3 treatment groups (150 mg, 600 mg, and 1800 mg elezanumab via intravenous infusion) and 1 placebo group to determine safety and tolerability in 20 patients with relapsing forms of MS. Adverse events (AEs), cerebrospinal fluid (CSF) and plasma biomarker analyses, and Expanded Disability Status Scale (EDSS) scores were assessed. Increasing levels of elezanumab were associated with decreased free soluble RGMa and increased interleukin-10 in CSF. EDSS scores were unchanged. Overall, elezanumab was well tolerated, with the most common AE being headache, and treatment did not consistently result in symptom worsening in patients who received multiple doses up to 1800 mg.

Elezanumab was granted orphan drug and fast track designations by the FDA on September 28, 2020, for treatment of spinal cord injuries. Two long-term, phase 2 studies are underway to elucidate the efficacy of elezanumab in larger patient populations. The RADIUS-R trial (NCT03737851), which commenced in December 2018, enrolled 208 participants with relapsing forms of MS. The RADIUS-P trial (NCT03737812), which began in February 2019, enrolled 123 participants with progressive forms of MS. Both randomized, double-blind, placebo-controlled, multiple-dose studies are assessing the safety and efficacy of elezanumab when added to standard of care and have an estimated study completion date of October 2021. In both trials, patients are randomly assigned to receive 1 of 2 doses of either elezanumab or placebo by intravenous infusion every 4 weeks for 48 weeks. Improvement in measures of physical disability (EDSS, Timed 25-Foot Walk, and 9-Hole Peg Test scores) is recorded at week 52 as the primary outcome.

Therapeutic antibodies are especially effective for diseases with clearly elucidated molecular mechanisms for which the specific molecules involved in pathogenesis have been identified. Despite its demonstrated efficacy, anti-RGMa mAb therapy does not address some aspects of MS progression, suggesting complexities in the mechanisms of this disease that may not be fully dependent on RGMa. The MS therapeutics market currently has multiple late-stage pipeline products with diverse mechanisms of action (eg, antioxidant; the mAb opicapumab, which inhibits LINGO-1, a negative regulator of axonal myelination; and sodium channel blockers). RGMc-based therapy is also a promising avenue worth exploring. RGMc, a member of the RGM family whose expression is limited to striated muscle and the liver, is downregulated in the sera of mice induced with EAE. Treatment with soluble RGMc enhanced the integrity of the blood-brain barrier to significantly delay the onset of EAE and reduce its clinical severity. Overall, with each new intervention undergoing development, investigators will gain further insight into the disease process of MS and eventually pinpoint the key molecular drivers of this disease.

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REFERENCES
ZEPOSIA—FOCUSED ON WHAT COUNTS

ZEPOSIA was studied in the largest number of patients with RMS in 2 pivotal head-to-head trials against an active comparator (N=2659).2,3a

<table>
<thead>
<tr>
<th>POWERFUL Efficacy</th>
<th>COMPARABLE Safety Profile vs Avonex</th>
<th>The FIRST AND ONLY SIP With No First-Dose Observation Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven superior in reducing relapses vs Avonex</td>
<td>Consistently low discontinuation rates vs Avonex</td>
<td>Full Prescribing Information for ZEPOSIA has NO FIRST-DOSE OBSERVATION required</td>
</tr>
<tr>
<td>Proven superior in reducing GdE and T2 lesions vs Avonex</td>
<td>Comparable rates of serious infections and malignancies vs Avonex</td>
<td>NO genetic testing required</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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-ug intramuscular injection. Primary endpoint: ZEPOSIA reduced ARR vs Avonex by 48% at 1 year (0.18 vs 0.35, respectively) and by 38% at 2 years (0.17 vs 0.28, 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.1,5

bAdverse 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 23%); hepatic transaminase elevation, 10% (vs 5%); 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, rhinitis, respiratory tract infection viral, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis. Hepatic transaminase elevation includes alanineaminotransferase increased, gamma-glutamyltransferase increased, aspartateaminotransferase increased, hepatic enzyme increased, liverfunction test abnormal, and transaminase increased. Hypertension includes hypertension, essential hypertension, and orthostatic hypertension. Overall discontinuation rates for ZEPOSIA vs Avonex at 1 year were 6% and 8%, respectively, and at 2 years were 10% and 15%, respectively. Discontinuation rates due to adverse reactions for ZEPOSIA vs Avonex at 1 year were 2.9% and 3.6%, respectively, and at 2 years were 3.0% and 4.1%, respectively. Serious infections: The rate of serious infections at 1 year for ZEPOSIA was 11% vs 0.7% for Avonex and the rate at 2 years for ZEPOSIA was 0.9% vs 0.9% for Avonex. Malignancy rates: The rate of malignancies at 1 year for ZEPOSIA was 0.9% vs 0.9% for Avonex.1,5 |

Indication
ZEPOSIA 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.

IMPORTANT SAFETY INFORMATION

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 or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial, unless the patient has a functioning pacemaker
- Patients with severe untreated sleep apnea
- Patients taking a monoamine oxidase (MAO) inhibitor

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

**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), or 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.

- **Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another SIP receptor modulator.** If CM is suspected, ZEPOSIA should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

- **Progressive Multifocal Leukoencephalopathy (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.** No cases of PML were identified in active-controlled MS clinical trials with ZEPOSIA. PML has been reported in patients treated with SIP receptor modulators 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.

- **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.

*A relapse was defined as the occurrence of new or worsening neurological symptoms persisting for more than 24 hours attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days.*

*Before initiating treatment with ZEPOSIA, all patients require a recent CBC including lymphocyte count (within 6 months or after discontinuation of prior MS therapy), an ECG to check for preexisting conduction abnormalities, a recent liver function test (within 6 months), and consideration of current and prior medications, including vaccinations. Patients without a confirmed history of varicella (chickenpox) or without documented VZV vaccination should be tested for antibodies. If VZV or other live attenuated immunizations are required, administer at least 1 month prior to initiation. For patients with a history of uveitis or macular edema, an ophthalmic assessment is required. An up-titration scheme should be used to reach the maintenance dosage of ZEPOSIA, as a transient decrease in heart rate and atrioventricular conduction delays may occur.*

**ARR**=annualized relapse rate; **CBC**=complete blood count; **ECG**=electrocardiogram; **GdE**=gadolinium enhancing; **RMS**=relapsing multiple sclerosis; **SIP**=sphingosine 1-phosphate; **VZV**=varicella-zoster virus.
IMPORTANT SAFETY INFORMATION (CONTINUED)

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 sinoatrial 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 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 ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation and regular follow-up examinations. An ophthalmic 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 unexpected neurological or psychiatric symptoms or any symptom/sign 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 Disability After Stopping ZEPOSIA: 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.

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

References:

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ZEPOSIA® (ozanimod) capsules, for oral use

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

1 INDICATIONS AND USAGE

ZEPOSIA 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.

2 DOSAGE AND ADMINISTRATION

2.1 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 (5.1)].

- **Cardiac Evaluation**
  Obtain an electrocardiogram (ECG) to determine whether preexisting conduction abnormalities are present. In patients with certain preexisting conditions, advice from a cardiologist should be sought [see Warnings and Precautions (5.2)].

- **Liver Function Tests**
  Obtain recent (i.e., within the last 6 months) transaminase and bilirubin levels [see Warnings and Precautions (5.3)].

- **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 (5.7)].

**Current or Prior Medications**

- If patients are taking anti-neoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of or use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with ZEPOSIA [see Warnings and Precautions (5.1) and Drug Interactions (7.1)].
- **Determine if patients are taking drugs that could slow heart rate or atrioventricular conduction** [see Warnings and Precautions (5.2) and Drug Interactions (7.2)].

**Vaccinations**

- Test patients for antibodies to varicella zoster virus (VZV) before initiating ZEPOSIA; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with ZEPOSIA [see Warnings and Precautions (5.1) and Drug Interactions (7.3)].

If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA.

2.2 Dosing Information

**Maintenance Dose**

After initial titration (see Treatment Initiation), the recommended maintenance dosage of ZEPOSIA is 0.92 mg taken orally once daily starting on Day 8.

ZEPOSIA capsules should be swallowed whole and can be administered with or without food.

**Treatment Initiation**

Initiate ZEPOSIA with a 7-day titration, as shown in Table 1 [see Warnings and Precautions (5.2)].

| Days 1-4 | 0.23 mg once daily |
| Days 5-7 | 0.46 mg once daily |
| Day 8 and thereafter | 0.92 mg once daily |

**2.3 Reinitiation of ZEPOSIA After Treatment Interruption**

If a dose of ZEPOSIA is missed during the first 2 weeks of treatment, reinitiate treatment using the titration regimen [see Dosage and Administration (2.2)].

If a dose of ZEPOSIA is missed after the first 2 weeks of treatment, continue with the treatment as planned.

4 CONTRAINDICATIONS

ZEPOSIA is contraindicated in patients who:

- **In the last 6 months, have experienced a myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III or IV heart failure** [see Warnings and Precautions (5.2)].
- **Have the 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** [see Warnings and Precautions (5.2)].
- **Have severe untreated sleep apnea** [see Warnings and Precautions (5.2)].
- **Are taking a monoamine oxidase (MAO) Inhibitor** [see Drug Interactions (7.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Infections

**Risk of Infections**

ZEPOSIA causes a mean reduction in peripheral blood lymphocyte count to 45% of baseline values because of the reversible sequestration of lymphocytes in lymphoid tissues [see Clinical Pharmacology (12.2)]. ZEPOSIA may therefore increase the susceptibility to infections, some serious in nature. 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.

In Study 1 and Study 2, the overall rate of infections and rate of serious infections in patients treated with ZEPOSIA was similar to that in patients who received interferon (IFN) beta-1a (35% vs 34% and 1% vs 0.8%, respectively). ZEPOSIA increased the risk of viral upper respiratory tract infections, urinary tract infections, and herpes zoster [see Adverse Reactions (6.1)].

The proportion of patients who experienced lymphocyte counts less than 0.2 x 10^9/L was 3.3%. These values generally returned to greater than 0.2 x 10^9/L while patients remained on treatment with ZEPOSIA. After discontinuing ZEPOSIA 0.92 mg, the median time for peripheral blood lymphocytes to return to the normal range was 36 days, with approximately 90% of patients in the normal range within 3 months [see Clinical Pharmacology (12.2)].

Consider interruption of treatment with ZEPOSIA if a patient develops a serious infection. Because the elimination of ZEPOSIA after discontinuation may take up to 3 months, continue monitoring for infections throughout this period.

**Hepatic Viral Infection**

In Study 1 and Study 2, herpes zoster was reported as an adverse reaction in 0.6% of patients treated with ZEPOSIA 0.92 mg and in 0.2% of patients who received IFN beta-1a. Herpes simplex encephalitis and varicella zoster meningitis have been reported with spongiosine 1-phosphate (S1P) receptor modulators. Patients without a healthcare professional-confirmed history of varicella (chickenpox), or without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating ZEPOSIA [see Vaccinations below].

**Cryptococcal Infection**

Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with S1P receptor modulators. Physicians should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. ZEPOSIA treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or cluminess of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

PML has been reported in patients treated with S1P receptor modulators and other multiple sclerosis (MS) therapies and has been associated with some risk factors (e.g., Immunocompromised patients, polyclonal non-immunosuppressants). Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, treatment with ZEPOSIA should be suspended until PML has been excluded by an appropriate diagnostic evaluation.

If PML is confirmed, treatment with ZEPOSIA should be discontinued.

Prior and Concomitant Treatment with Anti-neoplastic, Immunosuppressive, or Immune-modulating Therapies

In clinical studies, patients who received ZEPOSIA were not to receive concomitant treatment with anti-neoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for the treatment of MS. Concomitant use of ZEPOSIA with any of these therapies would be expected to increase the risk of immunosuppression. Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be co-administered with caution because of the risk of additive immune system effects during such therapy. When switching to ZEPOSIA from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects.

**Vaccinations**

Patients without a healthcare professional-confirmed history of chickenpox or without documentation of a full course of vaccination against 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, following which initiation of treatment with ZEPOSIA should be postponed for 4 weeks to allow the full effect of vaccination to occur.

No clinical data are available on the efficacy and safety of vaccinations in patients taking ZEPOSIA. Vaccinations may be less effective if administered during ZEPOSIA treatment.

If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA. Avoid the use of live attenuated vaccines during and for 3 months after treatment with ZEPOSIA.

5.2 Bradycardia and Atrioventricular Conduction Delays

Since initiation of ZEPOSIA may result in a transient decrease in heart rate and atrioventricular conduction delays, an up-titration scheme should be used to reach the maintenance dosage of ZEPOSIA [see Dosage and Administration (2.2) and Clinical Pharmacology (12.2)]. ZEPOSIA was not studied in patients who had:

- A myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization within the last 6 months
- New York Heart Association Class III / IV heart failure
- Cardioconduction or rhythm disorders, including sick sinus syndrome, significant QT prolongation (QTc > 450 msec in males, > 470 msec in females), risk factors for QT prolongation, or other conduction abnormalities or cardiac condition that in the opinion of the treating investigator could jeopardize the patient’s health
- Other pre-existing stable cardiac conditions without clearance from a cardiologist

**Fainting**

- Severe untreated sleep apnea
- A resting heart rate less than 55 beats per minute (bpm) at baseline

Reduction in Heart Rate

Initiation of ZEPOSIA may result in a transient decrease in heart rate. In Study 1 and Study 2, after the initial dose of ZEPOSIA 0.23 mg, the greatest mean decrease from baseline in heart rate of 1.2 bpm occurred at Hour 5 on Day 1, returning to near baseline at Hour 6. With continued up-titration, the maximal heart rate effect of ozanimod occurred on Day 8. The utility of performing first-dose cardiac monitoring when initiating ZEPOSIA in patients with characteristics similar to those studied in the clinical trials of ZEPOSIA is unclear. Heart rates below 40 bpm were not observed.

Initiation of ZEPOSIA without titration may result in greater decreases in heart rate [see Dosage and Administration (2.2)].
ZEPOSIA® [ozanimod] capsules, for oral use

In Study 1 and Study 2, bradycardia was reported on the day of treatment initiation in 0.6% of patients treated with ZEPOSIA compared to no patients who received IFN beta-1a. After Day 1, the incidence of bradycardia was 0.8% in patients treated with ZEPOSIA compared to 0.7% of patients who received IFN beta-1a.

Atrioventricular Conduction Delays

Initiation of ZEPOSIA may result in transient atrioventricular conduction delays. At ZEPOSIA exposures higher than the recommended dosage without dose titration, first- and second-degree type 1 atrioventricular blocks were observed in healthy volunteers; however, in Study 1 and Study 2 with dose titration, second- or third-degree atrioventricular blocks were not reported in patients treated with ZEPOSIA.

If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought for those individuals:

- With significant QT prolongation (QTc > 450 msec in males, > 470 msec in females)
- With arrhythmias requiring treatment with Class 1a or Class 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 with second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sinoatrial heart block [see Contraindications (4)]

5.3 Liver Injury

Elevations of aminotransferases may occur in patients receiving ZEPOSIA. Obtain transaminase and bilirubin levels, if not recently available (i.e., within 6 months), before initiation of ZEPOSIA. In Study 1 and Study 2, elevations of ALT to 5-fold the upper limit of normal (ULN) or greater occurred in 1.6% of patients treated with ZEPOSIA 0.92 mg and 1.3% of patients who received IFN beta-1a. Elevations of 3-fold the ULN or greater occurred in 5.5% of patients treated with ZEPOSIA and 3.1% of patients who received IFN beta-1a. The median time to an elevation of 3-fold the ULN was 6 months. The majority (79%) of patients continued treatment with ZEPOSIA with values returning to less than 3 times the ULN within approximately 2-4 weeks.

In clinical trials, ZEPOSIA was discontinued for a confirmed elevation greater than 5-fold the ULN. Overall, the discontinuation rate because of elevations in hepatic enzymes was 1.1% of patients treated with ZEPOSIA 0.92 mg and 0.8% of patients who received IFN beta-1a. Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice, and/or dark urine, should have hepatic enzymes checked, and ZEPOSIA should be discontinued if significant liver injury is confirmed.

Individuals with an AST or ALT greater than 1.5 times ULN were excluded from Study 1 and Study 2. Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking ZEPOSIA, caution should be exercised when using ZEPOSIA in patients with a history of significant liver disease.

5.4 Fetal Risk

There are no adequate and well-controlled studies in pregnant women. Based on animal studies, ZEPOSIA may cause fetal harm [see Use in Specific Populations (8.1)]. Because it takes approximately 3 months to eliminate ZEPOSIA from the body, women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for 3 months after stopping ZEPOSIA [see Use in Specific Populations (8.1)].

5.5 Increased Blood Pressure

In 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 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 150 mg) of tyramine could cause severe hypertension because of potential tyramine interaction in patients taking ZEPOSIA, even at 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.

5.6 Respiratory Effects

Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV1) were observed in patients treated with ZEPOSIA early as 3 months after treatment initiation. In 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 between patients treated with ZEPOSIA and patients who received IFN beta-1a was 1.9% (95% CI: -2.9, -0.8). Dose-dependent reductions in forced vital capacity (FVC) (absolute value and % predicted) were also seen at Month 3 in pooled analyses comparing patients treated with ZEPOSIA to patients who received IFN beta-1a (60 mL, 95% CI: -110, -10; 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 discontinued ZEPOSIA because of dyspnea. Spirometric evaluation of respiratory function should be performed during therapy with ZEPOSIA, if clinically indicated.

5.7 Macular Edema

S1P modulators, including ZEPOSIA, have been associated with an increased risk of macular edema. In 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 MS patients with a history of uveitis. In addition to the examination of the fundus, including the macula, prior to treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

5.8 Posterior Reversible Encephalopathy Syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a S1P receptor modulator. In controlled clinical trials with ZEPOSIA, one case of PRES was reported. Should a ZEPOSIA-treated patient develop any unexpected neurological or psychiatric symptoms/signs (e.g., cognitive deficits, behavioral changes, cortical visual disturbances, or any other neurological cortical symptoms/signs), any symptom/sign 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.

5.9 Unintended Additive Immunosuppressive 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 altemuzumab is not recommended [see Drug Interactions (7.1)].

5.10 Severe Increase in Disability After Stopping ZEPOSIA

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. Patients should be observed for a severe increase in disability upon ZEPOSIA discontinuation and appropriate treatment should be instituted, as required.

5.11 Immune System Effects After Stopping ZEPOSIA

After discontinuing ZEPOSIA, the median time for peripheral blood lymphocytes to return to the normal range was 30 days, with approximately 90% of patients in the normal range within 3 months [see Clinical Pharmacology (12.2)]. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore caution should be advised when initiating other drugs 4 weeks after the last dose of ZEPOSIA [see Drug Interactions (7.1)].

6 ADVERSE REACTIONS

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

- Infections [see Warnings and Precautions (5.1)]
- Bradycardia and Atrioventricular Conduction Delays [see Warnings and Precautions (5.2)]
- Liver Injury [see Warnings and Precautions (5.3)]
- Fetal Risk [see Warnings and Precautions (5.4)]
- Increased Blood Pressure [see Warnings and Precautions (5.5)]
- Respiratory Effects [see Warnings and Precautions (5.6)]
- Macular Edema [see Warnings and Precautions (5.7)]
- Posterior Reversible Encephalopathy Syndrome [see Warnings and Precautions (5.8)]
- Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Drugs [see Warnings and Precautions (5.9)]
- Severe Increase in Disability After Stopping ZEPOSIA [see Warnings and Precautions (5.10)]
- Immune System Effects After Stopping ZEPOSIA [see Warnings and Precautions (5.11)]

6.1 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.

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)].

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, urination, renal tract infection, back pain, and hypertension.
Table 2: Adverse Reactions with an Incidence of at Least 2% in ZEPOSIA-Treated Patients and at Least 1% Greater than IFN beta-1a (Pooled Study 1 and Study 2)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ZEPOSIA 0.92 mg (n=882)</th>
<th>IFN beta-1a 30 mcg Intramuscularly Once Weekly (n=885)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Upper respiratory infectiona</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Hepatic transaminase elevationb</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Back pain</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hypertensionb</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

a Data are not an adequate basis for comparison of rates between ZEPOSIA and the active control.
b Includes the following terms: nasopharyngitis, upper respiratory tract infection, pharyngitis, respiratory tract infection, bronchitis, rhinitis, respiratory tract infection viral, viral upper respiratory tract infection, rhinorrhea, tracheitis, and laryngitis.

7.1 Anti-Neoplastic, Immune-Modulating, or Immunosuppressive Therapies

Hypersensitivity, including rash and urticaria, has been reported with ZEPOSIA in active-controlled studies. An increased risk of cutaneous malignancies has been reported with another S1P receptor modulator.

7.2 Anti-Arhythmic Drugs, QT Prolonging Drugs, Drugs That May Decrease Heart Rate

ZEPOSIA has not been studied in patients taking QT prolonging drugs.

Class Ia (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) anti-arrhythmic drugs have been associated with cases of torsades de Pointes in patients with bradycardia. If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought.

7.3 Vaccination

During, and for up to three months after, discontinuation of treatment with ZEPOSIA, vaccinations may be less effective. The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during ZEPOSIA treatment and for up to 3 months after discontinuation of treatment with ZEPOSIA.

7.4 Strong CYP2C8 Inhibitors

Co-administration of ZEPOSIA with strong CYP2C8 inhibitors increases the exposure of the active metabolites of ozanimod (see Clinical Pharmacology (12.3)), which may increase the risk of ZEPOSIA adverse reactions. Therefore, co-administration of ZEPOSIA with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended.

7.5 Breast Cancer Resistance Protein (BCRP) Inhibitors

Co-administration of ZEPOSIA with BCRP inhibitors increases the exposure of the active metabolites of ozanimod (see Clinical Pharmacology (12.3)), which may increase the risk of ZEPOSIA adverse reactions. Therefore, co-administration of ZEPOSIA with inhibitors of BCRP (e.g., cyclosporine, etoricoxib) is not recommended.

7.6 Strong CYP2C6 Inhibitors

Co-administration of ZEPOSIA with strong CYP2C6 inducers (e.g., rifampin) reduces the exposure of the major active metabolites of ozanimod (see Clinical Pharmacology (12.3)), which may decrease the efficacy of ZEPOSIA. Therefore, co-administration of ZEPOSIA with strong CYP2C6 inducers should be avoided.

7.7 Monoamine Oxidase (MAO) Inhibitors

Co-administration of ZEPOSIA with MAO-B inhibitors may decrease exposure of the active metabolites of ozanimod. In addition, metabolites of ozanimod can inhibit MAO-B (see Clinical Pharmacology (12.3)). The potential for a clinical interaction with MAO inhibitors has not been studied; however, the increased risk of nonselective MAO inhibition may lead to a hypertensive crisis. Therefore, co-administration of ZEPOSIA with MAO inhibitors (e.g., selegiline, phenelzine, linezolid) is contraindicated. At least 14 days should elapse between discontinuation of ZEPOSIA and initiation of treatment with MAO inhibitors.

7.8 Adrenergic and Serotonergic Drugs

Because an active metabolite of ozanimod inhibits MAO-B in vitro, there is a potential for serious adverse reactions, including hypertensive crisis. Therefore, co-administration of ZEPOSIA with drugs or over-the-counter medications that can increase norepinephrine or serotonin (e.g., opioid drugs, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), tricyclics, tyramine) is not recommended. Monitor patients for hypertension with concomitant use.

Opioid Drugs

Serious, sometimes fatal reactions have been precipitated with concomitant use of opioid drugs (e.g., meperidine and its derivatives, methadone, or tramadol) and MAOIs, including selective MAO-B inhibitors. Although a small number of patients treated with ZEPOSIA were concomitantly exposed to opioids, this exposure was not adequate to rule out the possibility of an adverse reaction from co-administration.

7.9 Tyramine

MAO in the gastrointestinal tract and liver (primarily type A) provides protection from exogenous amines (e.g., tyramine). If tyramine were absorbed intact, it could lead to severe hypertension, including hypertensive crisis. Aged, fermented, cured, smoked, and pickled foods containing large amounts of exogenous amines (e.g., aged cheese, pickled herring) may cause release of norepinephrine resulting in a rise in blood pressure (tyramine reaction). Patients should be advised to avoid foods containing a large amount of tyramine while taking recommended doses of ZEPOSIA.

7.10 Sympathomimetic Medications

Concomitant use of ZEPOSIA with pseudoephedrine did not potentiate the effects on blood pressure (see Clinical Pharmacology (12.3)). However, hypertensive crisis has occurred with administration of ZEPOSIA alone (see Warnings and Precautions (5.5)) and hypertensive crisis has been reported with co-administration of other selective and nonselective MAO inhibitors (e.g., rasagiline) with sympathomimetic medications.

8 USE IN SPECIFIC POPULATIONS

8.1 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 (0.2, 0.1, 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/delayed 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 adverse effects on embryofetal development, plasma ozanimod exposure (AUC) for ozanimod was approximately 60 times that in humans at the maximum recommended human dose (MRHD) of 0.92 mg/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 (0.2, 0.6, or 2.0 mg/kg/day) to female rats during organogenesis resulted in a marked increase in embryofetal mortality at the highest dose tested and increased fetal malformations ( malformed blood vessels) and skeletal variations at the mid and high doses. Maternal toxicity was not observed. At the no-effect dose (0.2 mg/kg/day) for adverse effects on embryofetal development, plasma ozanimod exposure (AUC) was approximately 2 times that in humans at the MRHD; plasma AUCs for major human metabolites, CC112273 and CC1084037, were less than those in humans at the MRHD.

Oral administration of ozanimod (0.2, 0.7, or 2 mg/kg/day) to female rats throughout gestation and lactation resulted in persistent body weight reductions and long-term effects on reproductive (prolonged estrus cycle) and neurobehavioral (increased motor activity) function in offspring at the highest dose tested, which was not associated with maternal toxicity. At the no-effect dose (0.7 mg/kg/day) for adverse effects on pre- and postnatal development, plasma ozanimod exposure (AUC) was 30 times that in humans at the MRHD; plasma AUCs for major human metabolites, CC112273 and CC1084037, were less than those in humans at the MRHD.

8.2 Lactation

Risk Summary

There are not data on the presence of ozanimod in human milk, the effects on the breastfed infant, or the effects of the drug on milk production.

Concomitant administration of ZEPOSIA with MAO-B inhibitors may decrease exposure of the active metabolites of ozanimod. In addition, metabolites of ozanimod can inhibit MAO-B (see Clinical Pharmacology (12.3)).
**8.4 Pediatric Use**
Safety and effectiveness in pediatric patients have not been established.

**8.5 Geriatric Use**
Clinical studies of ZEPOSIA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**8.6 Hepatic Impairment**
The effect of hepatic impairment on the pharmacokinetics of the ozanimod major active metabolites is unknown (see Clinical Pharmacology (12.3)). Use of ZEPOSIA in patients with hepatic impairment is not recommended.

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**
Carcinogenesis
Oral administration of ozanimod (0, 8, 25, or 80 mg/kg/day) to Tg.rasH2 mice for 26-weeks resulted in an increase in hemangioma and hemangiosarcoma (combined) in males and females at the mid and high doses tested.

Oral administration of ozanimod (0, 0.2, 0.7, or 2 mg/kg/day) to rats for 2 years resulted in no increase in tumors. At the highest dose tested (2 mg/kg/day), plasma exposure (AUC) for ozanimod was approximately 100 times that in humans at the maximum recommended human dose (MRHD) of 0.92 mg/day. Plasma AUCs for major human metabolites, CC112273 and CC1084037, were similar to and less than, respectively, those in humans at the MRHD.

Mutagenesis
Ozanimod was negative in a battery of in vitro (Ames, mouse lymphoma tk) and in vivo (rat micronucleus) assays. Metabolite CC112273 was negative in in vitro (Ames, chromosomal aberration in mammalian cell) assays. Metabolite CC1084037 was negative in an Ames assay, and positive in an in vitro chromosomal aberration assay in human (TK6) cells but negative in an in vivo rat micronucleus/comet assay.

Impairment of Fertility
Oral administration of ozanimod (0, 0.2, 2, or 30 mg/kg/day) to male and female rats prior to and during mating and continuing through gestation day 7 resulted in no adverse effects on fertility. At the highest dose tested (30 mg/kg/day), plasma ozanimod exposure (AUC) was approximately 1600 times that in humans at the maximum recommended human dose (MRHD) (0.92 mg/day); plasma AUCs for metabolites, CC112273 and CC1084037, at 30 mg/kg/day were 13 and 3 times, respectively, those in humans at the MRHD.

**17 PATIENT COUNSELING INFORMATION**
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

**Risk of Infections**
Inform patients that they may be more likely to get infections, some of which could be life-threatening, when taking ZEPOSIA and for 3 months after stopping it, and that they should contact their healthcare provider if they develop symptoms of infection [see Warnings and Precautions (5.1)]. Inform patients that prior or concomitant use of drugs that suppress the immune system may increase the risk of infection. Advise patients that some vaccines containing live virus (live attenuated vaccines) should be avoided during treatment with ZEPOSIA. If immunizations are planned, administer at least 1 month prior to initiation of ZEPOSIA. Avoid the use of live attenuated vaccines during and for 3 months after treatment with ZEPOSIA. Patients without a healthcare professional-confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating ZEPOSIA.

**Cardiac Effects**
Advise patients that initiation of ZEPOSIA treatment may result in a transient decrease in heart rate. Inform patients that to reduce this effect, dose titration is required. Advise patients that the dose titration is also required if a dose is missed for 1 day or more during the first 14 days of treatment [see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.2)].

**Liver Injury**
Inform patients that ZEPOSIA may increase liver enzymes. Advise patients that they should contact their healthcare provider if they have any unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine [see Warnings and Precautions (5.3)].

**Pregnancy and Fetal Risk**
Inform patients that, based on animal studies, ZEPOSIA may cause fetal harm. Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant. Advise women of childbearing potential of the need for effective contraception during treatment with ZEPOSIA and for 3 months after stopping ZEPOSIA. Advise a female patient to immediately inform her healthcare provider if she is pregnant or planning to become pregnant [see Warnings and Precautions (5.4)].

**Respiratory Effects**
Advise patients that they should contact their healthcare provider if they experience new onset or worsening dyspnea [see Warnings and Precautions (5.5)].

**Macular Edema**
Advise patients that ZEPOSIA may cause macular edema, and that they should contact their healthcare provider if they experience any changes in their vision. Inform patient with diabetes mellitus or a history of uveitis that their risk of macular edema maybe increased [see Warnings and Precautions (5.7)].

**Posterior Reversible Encephalopathy Syndrome**
Advise patients to immediately report to their healthcare provider any symptoms involving sudden onset of severe headache, altered mental status, visual disturbances, or seizure. Inform patients that delayed treatment could lead to permanent neurological consequences [see Warnings and Precautions (5.8)].

**Severe Increase in Disability After Stopping ZEPOSIA**
Inform patients that severe increase in disability has been reported after discontinuation of a S1P receptor modulator like ZEPOSIA. Advise patients to contact their physician if they develop worsening symptoms of MS following discontinuation of ZEPOSIA [see Warnings and Precautions (5.10)].

**Immune System Effects After Stopping ZEPOSIA**
Advise patients that ZEPOSIA continues to have effects, such as lowering effects on peripheral lymphocyte count, for up to 3 months after the last dose [see Warnings and Precautions (5.11)].

Manufactured for: Celgene Corporation
Summit, NJ 07901

Patent: www.celgene.com/therapies

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The Global Push for Mechanical Thrombectomy in Stroke Care

Increasing the use and accessibility of mechanical thrombectomy may reduce the burden of stroke on a global scale.

By Matt Hoffman

Q. What prompted the initiation of MT2020+?

IN THE LAST DECADE, mechanical thrombectomy has proven to be an efficacious and cost-effective approach to treating stroke.1,2 Despite this, its use has been relatively limited on a global scale.

As such, members of the Society of Vascular and Interventional Neurology’s (SVIN) global initiative, Mission Thrombectomy 2020+ (MT2020+), recently published a white paper calling for a push to increase awareness, accessibility, and action for mechanical thrombectomy for patients with stroke worldwide.3,4 The SVIN group ultimately called for 2 primary goals to be achieved: first, the implementation of public health interventions to double global access to mechanical thrombectomy treatments every 2 years for the next decade, and second, to perform 202,000 procedures worldwide by the end of 2020.

To better understand the goals of the initiative and need for increased use of this treatment, NeurologyLive® spoke with the chair of MT2020+, Dileep Yavagal, MD, professor of clinical neurology at the University of Miami and past president of SVIN.

Q. Is mechanical thrombectomy used widely enough in clinical practice where it is available?

It has actually increased quite rapidly, especially in the

DILEEP YAVAGAL, MD
Professor of Clinical Neurology, University of Miami
Chair, Mechanical Thrombectomy 2020+
Past president, Society of Vascular and Interventional Neurology

Q&A

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Q. What prompted the initiation of MT2020+?

In 2015, mechanical thrombectomy, as a surgical treatment for stroke, became standard of care for large vessel occlusion (LVO) stroke. This is the most severe form of stroke, where a large artery in the brain gets suddenly blocked by a clot that either comes from the heart or diseased arteries in the neck, sometimes the arch of the aorta, and results in significant disability, like loss of speech or loss of movement on one side of the body. The standard-of-care approval of this treatment really was a major step forward, not just in stroke, but all of medicine. The reason being that LVO stroke, as we know, accounts for anywhere from 15% to as high as 30% of all strokes, and its contribution to long-term disability burden and death is much higher. Of all stroke-related long-term disability and death, LVO stroke [accounts for] almost three-fifths of that burden. There’s a disproportionate contribution because of how severe these strokes are, and the fact that we now have a treatment that’s overwhelmingly powerful in reversing this is a major, aptly called revolution that has occurred.

When this happened in 2015, we started to think about implementation and dissemination of this treatment, not just all over the United States, but also globally. In researching that, I realized that the burden of stroke is actually disproportionately higher in low- and middle-income countries, [which] shoulder 80% of all stroke burden, whereas the high-income countries only have about 20% of all stroke. There are about 13.6 million strokes per year, and the vast majority of them are in under-resourced areas. To get mechanical thrombectomy to make a dent on the global stroke burden, we would really have to get this therapy to be available worldwide.

The therapy is effective up to 24 hours after stroke symptoms, so it has to be accessed very urgently. In the early period, it’s very time sensitive. The earlier you get this treatment, the better the outcomes. That’s putting 2 types of burden on accessing this care. It has to be available widely, but also in a geographically distributed manner so that patients can get it quickly. It’s not a therapy that affords itself to being centralized.
high-income countries, because it’s so overwhelmingly effective. Almost 50% of treated patients are completely independent at 3 months, which is very powerful compared to any therapy in medicine. But having said that, that rate of exponential increase still leaves a vast gap even in the US. In 2019, the estimate of thrombectomies was right below 40,000, whereas the number of patients who could benefit from thrombectomy was between 200,000 and 350,000. That gap is 5 times wider, or even more, in the low- and middle-income countries. So, while it’s widely practiced, while it’s increasing, the initial baseline gap is so high that even our metric of doubling the rate of thrombectomies every 2 years in a given region could only get us to fill 50% of the gap—we estimate in about 10 to 15 years. But if we didn’t even do public health interventions, it would probably be 30 or 40 years before we get to about 50% or 60% access. The rate is increasing, but it’s not fast enough.

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— DILEEP YAVAGAL, MD

Q: What factors affect the greater adoption of this more rapidly?

Because of the time sensitivity and the fact that you need to have a center that’s ready to do this 24/7, this treatment needs a system of care to be in place in a given community. So that places an additional system burden on a community. For something like, let’s say, the treatment of pneumonia, it doesn’t need a system. Because first of all, it’s widely known. Everybody knows it, the antibiotics are widely available, and there is time. You don’t have only 24 hours. You can access it. Then, let’s say that the pneumonia is very complicated. You can transfer to a [more specialized] center. For a condition like LVO stroke, it’s like a cardiac arrest, but of a part of the brain. If you don’t do CPR very quickly, you’re losing that part of the brain. So that need for a system to be in place is such a huge step, that unless this is proactively pursued by communities and by stakeholders, it’s going take a long time to just by itself fall in place.

Q: Is education about mechanical thrombectomy a challenge?

Absolutely. The education around the fact that LVO stroke should be recognized in the field and triaged to the right center is one big educational gap. That’s a prehospital system gap that needs to be addressed in a big way. The US is a vast country, and certainly, globally, we have a lot of area to cover. The second big gap is this understanding that a fair number of resources and thought need to be put into building a strong system of care in our community, and in a hospital, to really make this happen to get the best outcomes. Those are the 2 educational pieces: one is prehospital, and one is the clinicians themselves.

Q: How does MT2020+ plan to help close that gap?

Public health interventions are the approach that MT2020+ is using to achieve our goals. By that what we mean is using upstream strategies—going from a big picture approach, rather than going hospital by hospital, because the efficiency of public health interventions is much higher in increasing access suddenly. Things need to happen from the ground up also, but the health policy makers really need to be fully educated about the benefit of thrombectomy and thrombectomy systems.

The second public health intervention that has a common application is prehospital personnel education of recognizing LVOs. There are very standardized scales now, and the need to bring the patient as rapidly as possible to a thrombectomy center is apparent. The third is certification. To bring someone to a thrombectomy center, that thrombectomy center has to be recognized as such, and without certification, it’s a hit or miss. It’s not publicly known, especially at 3am when a stroke happens, where to take the patient. I would say there are probably about 10 very intense public health interventions that have an impact. These are the top 3 that I’ve mentioned. But the way we are doing it is we have created regional committees that are headed by a stroke neurologist and an interventionist in 82 regions in the world already. Those regional committees can actually decide what are the top 3 or 4 interventions that will make the most impact in a given year. For example, in low- and middle-income countries, reimbursement for these procedures and having no barrier for a concentration of reimbursement when the [need arises] are big public health interventions that need to be put in place, with either public system funding or some other mechanism of payment. The public interventions vary from region to region in terms of the most impact, but these would be examples of what is being perceived by MT2020+ as effective for any community around the globe.

The US is a leader in mechanical thrombectomy research and implementation, and this is a great opportunity to influence global health in a manner that could affect millions of people. The prevalence of stroke was estimated in 2017 to be over 100 million people. It’s a big burden that the US could influence as a leader by sharing best practices and influencing public policy, not just here, but around the world.

For a full list of references, see the article on NeurologyLive.com.
Discover a New Treatment for Dravet Syndrome

Watch an on-demand broadcast from NeurologyLive® and Zogenix featuring Dr. Kelly Knupp and Dr. M. Scott Perry as they discuss Dravet Syndrome and a new treatment option.

Join these experts:

Kelly Knupp, MD
Children’s Hospital
Colorado Aurora, CO

M. Scott Perry, MD
Cook Children’s Medical Center
Fort Worth, TX

In this broadcast, Dr. Knupp and Dr. Perry will:

- **Review** unmet needs in Dravet Syndrome
- **Assess** the clinical landscape
- **Discuss** safety and efficacy of a new therapeutic option

SCAN THE CODE BELOW TO WATCH NOW
Eisai Targets Dravet Syndrome Indication for Lorcaserin With Multifaceted Study Design

By Marco Meglio

LORCASERIN AIMS TO BECOME the next FDA-approved treatment for patients with Dravet syndrome. Developed by Eisai, the selective serotonin 5-HT2C receptor agonist will be used as an adjunctive treatment in the recently initiated phase 3 MOMENTUM 1 clinical study (Study 304; NCT04572243), which will evaluate the agent in patients with Dravet syndrome (DS) and is expected to be completed in December 2021. Additionally, Eisai announced it will continue the lorcaserin expanded access program through Study 405 (NCT04457687), also known as the MOMENTUM 2 study.1

It originally served as the primary ingredient in Belviq, a weight loss medication from Arena Pharmaceuticals. The CAMELLIA-TIMI 61 study (NCT02019264) indicated that the drug sustained weight loss without a higher rate of major cardiovascular events compared with placebo.2 However, it also showed an imbalance in the number of patients with malignancies, and lorcaserin was subsequently withdrawn from the market.1

At the time, Belviq maintained off-label use as a treatment for the disorder and other refractory epilepsies. Eisai noted that it had received multiple requests from patients, caregivers, and health care professionals for continued access to lorcaserin for patients who were prescribed Belviq to help treat DS and these refractory epilepsies. The requests prompted a consultation with the FDA, which agreed with Eisai about the importance of patient access to lorcaserin for DS. Furthermore, the agency noted that this access would be granted based on the extent of each individual’s health care provider’s belief in the continued access as medically appropriate.

The unique mechanism of action of lorcaserin as a selective serotonin 5-HT2C receptor agonist unsuppressed neuron firing in patients with DS. “Over 80% of cases are caused by a sodium channel mutation. That sodium channel mutation particularly impacts GABA (γ-aminobutyric acid) inhibitory interneurons. Those neurons can normally suppress firing, and it’s thought that when that inhabitation is released, it increases the susceptibility to seizures,” Michael Irizarry, PhD, vice president of clinical research at Eisai, told NeurologyLive®.

In a preclinical zebrafish model, lorcaserin was used to treat 5 patients with medically intractable DS and showed promising results in terms of reductions in seizure frequency and/or severity. Investigators noted a 65% reduction in seizure frequency during the first 3-month treatment period.1 “Because it’s specific to 5-HT2C, it doesn't have some of the same safety liabilities of other drugs that have valvular safety issues that more broadly target the serotonergic system,” Irizarry said.

Now, the focus shifts toward MOMENTUM 1, which has a target enrollment of 58 patients with DS who will be evaluated at approximately 20 sites in the United States. The study will evaluate the percent change in frequency of convulsive seizures per 28 days in patients taking lorcaserin compared with placebo (see FIGURE).

The percentage of 50% responders with convulsive seizures in the core treatment period compared to baseline will be used as a secondary outcome measure. In addition to efficacy, researchers will attempt to characterize the pharmacokinetics of lorcaserin and the relationships between lorcaserin plasma concentrations and efficacy and safety.

Patients in MOMENTUM 1 will be randomized to receive lorcaserin administered as an oral suspension twice daily for 14 weeks during the core treatment period. Dosage will be based on body weight as follows: target doses for participants weighing 10 kg to < 20 kg, 20 kg to < 40 kg, and ≥ 40 kg will be 5 mg, 10 mg, and 20 mg per day, respectively. Subjects must be aged 2 years or older at the time of informed consent, have a diagnosis of epilepsy with DS, had at least 4 convulsive seizures during the 4-week baseline period, be on a stable treatment regimen of antiepileptic drugs for at least 4 weeks pre-screening, and must be expected to remain stable throughout the study. Patients who used lorcaserin within 4 weeks or fenfluramine (Fintepla; Zogenix) within 2 months of screening, have recent or concomitant use of serotonergic medications or monoamine oxidase inhibitors, or have the presence of progressive central nervous system disease other than DS were excluded from the trial.

“Our intention would be to seek approval after this study. The way we’ve designed it, we’re looking for a large treatment effect. We believe that the safety is well understood; the key question will be the efficacy that’s determined,” Irizarry concluded.

MOMENTUM 2 will include patients with DS and other refractory epilepsies who were prescribed lorcaserin by their treating physician prior to the market withdrawal. The study will include a pharmacokinetics substudy, a retrospective chart review, and prospective data collection to gather information on seizure frequency, pharmacokinetics, and safety with lorcaserin exposure.}

![FIGURE. Phase 3 MOMENTUM 1 Trial to Evaluate Efficacy and Safety of Lorcaserin in Dravet Syndrome](NeurologyLive.com)
Data Evolution in Alzheimer Disease: Is the Future Digital?

Digital biomarkers offer promise to revolutionize the diagnosis and treatment of Alzheimer disease via our increasing ability to gather active and passive data.

By Nicola Davies, PhD

**ALZHEIMER DISEASE (AD) IS A** leading cause of disability and the fifth leading cause of death in patients age 65 or older.¹ As the aging population continues to grow, the incidence of AD also increases, spurring research into innovative ways of detecting, managing, and treating the condition. Digital biomarkers, in particular, have aroused interest from researchers and manufacturers, as they have the potential to provide precise, quantifiable physiological information that can be used as diagnostic and prognostic indicators.

**What Are Digital Biomarkers?**

Any medical data that are objectively collected through digital technology, such as wearable devices and smartphones, are referred to as “digital biomarkers.” Given that the wearable health care device market is predicted to grow by 20% in the next 5 years,² digital biomarker are an attractive option within the medical community.

Digital biomarkers show definite promise in detecting AD in its early stages.

“Although the gold standard for diagnosis is an autopsy or positron emission tomography (PET) scan, clinically validated end points for digital biomarkers are on their way,” said Graham Jones, PhD, director of innovation at Novartis. Indeed, over the past few years, much research has focused on the utility of digitally acquired data in detecting AD and predicting cognitive decline.

Based on their method of acquisition, 2 major categories of digital biomarkers are currently being employed for neurologic conditions³:

- **Active biomarkers**, as the name suggests, require users to be actively involved in recording the parameter being measured. These biomarkers generally assess cognitive function through digitally administered tests or quizzes.
- **Passively collected data**, on the other hand, occurs without active user engagement and results in continuous, real-time data acquisition. For instance, data such as step count, gait symmetry, and clarity of speech can all be recorded during spontaneous activities, and without any engagement on the part of the user.

**Cognitive Testing**

According to Mircea Balasa, MD, PhD, a neurologist at Hospital Clinic de Barcelona in Spain, innovative digital biomarkers based
on cognitive testing are being devised to improve on existing neuropsychological symptom tests, making them more standardized and reliable. One such innovation is using gamified versions of standard memory tests to make it more attractive and increase patient engagement. For example, Balasa and his team have been working on validating the Altoida Neuro Motor Index device, which is based on augmented reality technology and consists of a 10-minute gamified assessment that tests a patient’s functional and cognitive aptitude. “At present, the Altoida device shows promise in distinguishing patients with mild cognitive impairment from controls,” Balasa told NeurologyLive.

Central Nervous System Functioning
Research has shown that AD presents with a definitive decline in sensory and motor functioning, even before cognitive decline begins. These deficits include general visual parameters, such as visual acuity, color perception, contrast sensitivity, and visual integration, all of which are reduced in patients with mild AD. Investigators have suggested that passive tests can measure the amount of fixation time on certain graphics that are repeatedly viewed, to quantify visual parameters over time. Both peripheral and central auditory system dysfunction occur in the prodromal stages of AD, and passively monitoring conversations could be one way of screening for AD. For instance, a study showed that atypical repetitions in 2 conversations that occurred on different days was a strong indicator of AD. Reading comprehension can also be evaluated by tracking eye movements.

In addition, slow gait speed is a strong predictive factor for dementia and cognitive decline. Measurement of gait speed using an accelerometer or gyroscope sensors has the potential to improve the detection of AD. Also, touchscreen sensors can evaluate fine motor control capabilities such as typing skills, swiping, and other keystroke patterns.

Autonomic Nervous System Functioning
Imaging studies have shown that neuropathological lesions can develop in the autonomic nervous system (ANS) in the earliest stages of AD. “The ANS is fertile ground for diagnosis,” Jones told NeurologyLive. “The ANS impacts several factors that can be picked up by digital tools—heart rate, reflexes, and respiration, for instance.” Indeed, the earliest stages of AD have been associated with disturbed circadian rhythms, so devices that have built-in ballistocardiography sensors can be used to monitor sleep patterns.

Determining the Most Accurate Digital Biomarkers
Although investigators have studied a variety of digital biomarkers, very few have dealt with real-world, home-based evaluations. In 2019, Evidation Health set the ball rolling when they partnered with Apple and Eli Lilly and Company for a real-world study that produced around 16 terabytes of digital biomarker data. The investigators were able to establish that specific motor skills, such as reading, typing, and keystroke tasks were performed more slowly in patients who had mild cognitive impairment and dementia.

In 2018, the United Kingdom (UK) Alzheimer’s Society and the University of Oxford’s Big Data Institute launched the

<table>
<thead>
<tr>
<th>Device/app</th>
<th>Digital biomarker</th>
<th>Method of assessment</th>
<th>Category</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altoida device</td>
<td>• Cognitive function</td>
<td>• Gamified exercises</td>
<td>Active</td>
<td>FDA and CE approved, available for use by physicians.</td>
</tr>
<tr>
<td>Apple watch</td>
<td>• Gross motor function: through stairs climbed and hours of standing and walking</td>
<td>• Accelerometer, gyroscope, Heart rate sensor, Withdrawal from usual tasks and increased reliance on helper apps</td>
<td>Passive</td>
<td>Features are available; not licensed specifically for Alzheimer detection.</td>
</tr>
<tr>
<td>iPhone</td>
<td>• Gross motor function: o Walking o Sleep pattern o Cognitive function o Speech and language</td>
<td>• Pedometer, Energy survey, Mood survey, Audio/video recordings, Typing task</td>
<td>Passive</td>
<td>Features are available; not licensed specifically for Alzheimer detection.</td>
</tr>
<tr>
<td>Beddit sleep monitor</td>
<td>• Sleep patterns and circadian rhythm</td>
<td>• Sleep sensors</td>
<td>Passive</td>
<td>App available for iPhone.</td>
</tr>
<tr>
<td>Sea Hero Quest app</td>
<td>• Cognitive function</td>
<td>• Spatial navigation patterns</td>
<td>Active</td>
<td>App available for smart devices.</td>
</tr>
<tr>
<td>GameChanger/Mezurio</td>
<td>• Memory, thinking and learning function</td>
<td>• Gaming app</td>
<td>Active</td>
<td>Data from app is under the process of being validated.</td>
</tr>
<tr>
<td>Unnamed wearable device being developed by Early detection of Neurodegenerative diseases (EDoN) project</td>
<td>• Gross motor function o Fine motor function o Speech and language metrics o Eye movements o Heart rate variability</td>
<td>• Accelerometer, Swiping and typing sensors, Microphone, Camera, Heart rate sensors</td>
<td>Passive</td>
<td>Device under development; prototype expected to be ready in 3 years.</td>
</tr>
<tr>
<td>Altoida device</td>
<td>• Sleep patterns</td>
<td>• Sleep sensors</td>
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There is a very real expectation that digital biomarkers can monitor progression from prodromal to diseased states...[and] some evidence that learned behaviors—such as performing specific functions on tablets—coupled with certain exercise regimens, can delay the onset and severity of diseases like AD.
— GRAHAM JONES, PHD

Revolutionizing the Management of AD
Digital biomarkers have the potential to advance several stages of the disease process:

- **Earlier diagnosis:** The current standard for diagnosis of AD is through PET molecular imaging, which is expensive and often only available at regional facilities. In contrast, when patients use mobile or wearable devices, there is continuous monitoring of passive biomarkers and data can be compared to the patient’s previous data. This makes it easier to detect any decline in nervous system parameters. “Any deviations from normal biomarker levels can be used as an indication to recommend more specific investigations, such as PET scans,” Jones said.

- **Monitor high-risk individuals:** Currently, neuropsychological testing is used to monitor cognitive function in high-risk individuals. However, these tests are not always reliable and may fail to detect the earliest stages of cognitive impairment. According to Balasa, active digital biomarkers could be used instead to create prognostic models that can help monitor patients who are at higher risk of developing cognitive decline. “Such individuals do not normally seek medical advice, as they don’t usually have clinically relevant cognitive decline,” he said.

- **Optimize clinical trials:** Digital biomarkers are a cost-effective solution to collect objective, continuous, quantifiable data in a longitudinal manner. The precision of this data can increase the statistical power of clinical trials.

- **New opportunities for scientific study:** In the advanced stages of AD, neurons are destroyed and the opportunity to study disease pathology is limited. By identifying patients in the early stages of the disease via digital biomarkers, researchers can gain a deeper understanding of the pathophysiology of AD, which can help develop novel treatment strategies.

Challenges of Using Digital Biomarkers
Wearable devices still have a long way to go before they can be reliably used for the diagnosis and management of AD. “The issue for most of these devices is clinical validation with appropriate double-blind trials,” Jones said. For effective real-world usage, clinical validation needs to be followed by regulatory approval. The Altoida device is currently the only device specific for AD that has FDA approval and CE marking. While the Apple Watch has FDA approval for fall detection and ECG rhythm monitoring, its AD-specific features still need validation and approval.

Actively measured biomarkers require dedicated engagement on the part of the patient, who must manually enter inputs into the recording device. Lack of interest or even beginning memory loss are some challenges that can prevent the effective use of this kind of biomarker. While passive biomarkers do not face these challenges, the large volumes of data that are acquired create the need for extensive storage systems. Analysis of this data may require complex tools and trained personnel.

In addition to these disadvantages, both kinds of data face another challenge: wearable devices record vast amounts of medical data that must remain confidential. “We need to navigate data privacy and Health Insurance Portability and Accountability Act regulations,” said Jones. Some applications such as Apple Health allow users to access their health care data directly through their own devices, which may increase the need for secure access to such data.

The Future of Digital Biomarkers For AD
In Jones’ opinion, apart from timely diagnosis, there are 2 future directions that hold promise. The first is monitoring disease progression. “There is a very real expectation that digital biomarkers can monitor progression from prodromal to diseased states,” he said, adding that cognitive performance could also be tracked digitally. Secondly, and more promising, is the possibility of actual treatment using digital tools. “There is some evidence that learned behaviors—such as performing specific functions on tablets—coupled with certain exercise regimens, can delay the onset and severity of diseases like AD,” he said. Of course, these digital forms of treatment need sound exploration and validation before they become a reality.

For a full list of references, see the article on NeurologyLive.com.
patients with evidence of significant liver injury. or severe hepatic impairment. Consider not initiating EPIDIOLEX in slower dose titration is recommended in patients with moderate af act the liver (e.g., valproate or clobazam). Dose adjustment and discontinuation of EPIDIOLEX or concomitant medications known to concomitant valproate, or without dose reduction. For patients clinically indicated. Resolution of transaminase elevations occurred should be obtained prior to starting treatment, at one, three, and six Concomitant use of valproate and elevated transaminase levels EPIDIOLEX can cause dose-related transaminase elevations. Hepatocellular Injury: EPIDIOLEX (cannabidiol) oral solution is contraindicated in patients with a history of hypersensitivity to cannabidiol or any ingredients in the product. **WARNINGS & PRECAUTIONS** Hepatocellular Injury: EPIDIOLEX can cause dose-related transaminase elevations. Concomitant use of valproate and elevated transaminase levels at baseline increase this risk. Transaminase and bilirubin levels should be obtained prior to starting treatment, at one, three, and six months after initiation of treatment, and periodically thereafter, or as clinically indicated. Resolution of transaminase elevations occurred with discontinuation of EPIDIOLEX, reduction of EPIDIOLEX and/or concomitant valproate, or without dose reduction. For patients with elevated transaminase levels, consider dose reduction or discontinuation of EPIDIOLEX or concomitant medications known to affect the liver (e.g., valproate or clobazam). Dose adjustment and slower dose titration is recommended in patients with moderate or severe hepatic impairment. Consider not initiating EPIDIOLEX in patients with evidence of significant liver injury.

**Somnolence and Sedation:** EPIDIOLEX can cause somnolence and sedation that generally occurs early in treatment and may diminish over time; these effects occur more commonly in patients using clobazam and may be potentiated by other CNS depressants.

**Suicidal Behavior and Ideation:** Antiepileptic drugs (AEDs), including EPIDIOLEX, increase the risk of suicidal thoughts or behavior. Inform patients, caregivers, and families of the risk and advise to monitor and report any signs of depression, suicidal thoughts or behavior, or unusual changes in mood or behavior. If these symptoms occur, consider if they are related to the AED or the underlying illness.

**Please see additional Important Safety Information and Brief Summary of Prescribing Information on the following pages.**

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATION: HYPERSENSITIVITY**

EPIDIOLEX (cannabidiol) oral solution is contraindicated in patients with a history of hypersensitivity to cannabidiol or any ingredients in the product.
EPIDIOLEX has broad-spectrum efficacy, significantly reducing multiple seizure types in TSC, LGS, and Dravet syndrome

Demonstrated reductions in:
- TSC-associated seizures, including both partial-onset* and generalized seizures
- Drop/total seizures in LGS
- Convulsive seizures in Dravet syndrome

Can be prescribed in adults and children as early as 1 year of age across 3 indications

Sustained effects up to 3 years in open-label extensions in LGS and Dravet syndrome

Within 1 year on market, more than 15,000 patients in the US were treated with EPIDIOLEX by over 3000 prescribers

*Partial-onset seizures (focal) included simple partial seizures (focal motor seizure), complex partial seizures (focal impaired), and secondary generalized tonic-clonic seizures (focal to bilateral tonic-clonic).

Efficacy proven across 3 of the most difficult-to-treat epilepsies

Visit EPIDIOLEXhcp.com for more details

IMPORTANT SAFETY INFORMATION & INDICATIONS (cont’d)

WARNINGS & PRECAUTIONS (cont’d)

Withdrawal of Antiepileptic Drugs:
As with most AEDs, EPIDIOLEX should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus.

ADVERSE REACTIONS:
The most common adverse reactions in patients receiving EPIDIOLEX (≥10% and greater than placebo) include transaminase elevations; somnolence; decreased appetite; diarrhea; pyrexia; vomiting; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder and poor-quality sleep; and infections. Hematologic abnormalities were also observed.

PREGNANCY:
EPIDIOLEX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage women who are taking EPIDIOLEX during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry.

DRUG INTERACTIONS:
Strong inducers of CYP3A4 and CYP2C19 may affect EPIDIOLEX exposure. EPIDIOLEX may affect exposure to CYP2C19 substrates (e.g., clobazam, diazepam) or others. Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations. No drug interaction studies have been completed, but case reports suggest a potential for elevations of mammalian target of rapamycin (mTOR) or calcineurin inhibitors when used with EPIDIOLEX. Dosage adjustment of EPIDIOLEX or other concomitant medications may be necessary.

INDICATIONS:
EPIDIOLEX (cannabidiol) oral solution is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients 1 year of age and older.

Please see the Brief Summary of Prescribing Information on the following pages.

EPIDIOLEX® (cannabidiol) oral solution
Brief Summary of Prescribing Information
See package insert for full Prescribing Information (PI)
or visit www.EPIDIOLEXhcp.com
Rx only

INDICATIONS AND USAGE - EPIDIOLEX is indicated for the treatment of seizures associated with Lennox Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients 1 year of age and older.

CONTRAINDICATIONS - EPIDIOLEX is contraindicated in patients with a history of hypersensitivity to cannabidiol or any of the ingredients in the product [see Description and Warnings and Precautions in full PI].

WARNINGS AND PRECAUTIONS
Hepatocellular Injury - EPIDIOLEX can cause dose-related elevations of liver transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]). In controlled studies for LGS and DS (10 and 20 mg/kg/day dosages) and TSC (25 mg/kg/day) doses and TSC (25 mg/kg/day), the incidence of ALT elevations above 3 times the upper limit of normal (ULN) was 13% (10 and 20 mg/kg/day dosages) and 12% (25 mg/kg/day dosage) in EPIDIOLEX-treated patients compared with 1% in patients on placebo. Less than 1% of EPIDIOLEX-treated patients had ALT or AST levels greater than 20 times the ULN. There were cases of transaminase elevations associated with hospitalization in patients taking EPIDIOLEX. In clinical trials, serum transaminase elevations typically occurred in the first two months of treatment initiation; however, there were some cases observed up to 18 months after initiation of treatment, particularly in patients taking concomitant valproate. Resolution of transaminase elevations occurred with discontinuation of EPIDIOLEX or reduction of EPIDIOLEX and/or concomitant valproate in about two-thirds of the cases. In about one-third of the cases, transaminase elevations resolved during continued treatment with EPIDIOLEX, without dose reduction.

Risk Factors for Transaminase Elevation:
Concomitant Valproate and Clobazam - The majority of ALT elevations occurred in patients taking concomitant valproate. Concomitant use of clobazam also increased the incidence of transaminase elevations, although to a lesser extent than valproate [see Drug Interactions in full PI]. In EPIDIOLEX-treated patients with LGS or DS (10 and 20 mg/kg/day dosages), the incidence of ALT elevations greater than 3 times the ULN was 30% in patients taking both concomitant valproate and clobazam, 21% in patients taking concomitant valproate (without clobazam), 4% in patients taking concomitant clobazam (without valproate), and 3% in patients taking neither drug. In EPIDIOLEX-treated patients with TSC (25 mg/kg/day), the incidence of ALT elevations greater than 3 times the ULN was 20% in patients taking both concomitant valproate and clobazam, 25% in patients taking concomitant valproate (without clobazam), 0% in patients taking concomitant clobazam (without valproate), and 6% in patients taking neither drug. Consider discontinuation or dose adjustment of valproate or clobazam if liver enzyme elevations occur.

Dose - Transaminase elevations are generally dose-related. In patients with DS or LGS (10 and 20 mg/kg/day) or TSC (25 mg/kg/day), ALT elevations greater than 3 times the ULN were reported in 17% and 12% of patients taking EPIDIOLEX 20 or 25 mg/kg/day, respectively, compared with 1% in patients taking EPIDIOLEX 10 mg/kg/day. The risk of ALT elevations was higher (25%) in patients with TSC receiving a dosage above the recommended maintenance dosage of 25 mg/kg/day in Study 4.

Baseline Transaminase Elevations - Patients with baseline transaminase levels above the ULN had higher rates of transaminase elevations when taking EPIDIOLEX. In the DS and LGS controlled trials (Studies 1, 2, and 3) in patients taking EPIDIOLEX 20 mg/kg/day, the frequency of treatment-emergent ALT elevations greater than 3 times the ULN was 30% when ALT was above the ULN at baseline, compared to 12% when ALT was within the normal range at baseline. No patients taking EPIDIOLEX 10 mg/kg/day experienced ALT elevations greater than 3 times the ULN when ALT was above the ULN at baseline, compared with 2% of patients in whom ALT was within the normal range at baseline. In the TSC controlled trial (Study 4) in patients taking EPIDIOLEX 25 mg/kg/day, the frequency of treatment-emergent ALT elevations greater than 3 and 5 times the ULN were both 11% when ALT was above the ULN at baseline, compared to 12% and 6%, respectively, when ALT was within the normal range at baseline.

Monitoring: In general, transaminase elevations of greater than 3 times the ULN in the presence of elevated bilirubin without an alternative explanation are an important predictor of severe liver injury. Early identification of elevated liver enzymes may decrease the risk of a serious outcome. Patients with elevated baseline transaminase levels above 3 times the ULN, accompanied by elevations in bilirubin above 2 times the ULN, should be evaluated prior to initiation of EPIDIOLEX treatment. Prior to starting treatment with EPIDIOLEX, obtain serum transaminases (ALT and AST) and total bilirubin levels. Serum transaminases and total bilirubin levels should be obtained at 1 month, 3 months, and 6 months after initiation of treatment with EPIDIOLEX, and periodically thereafter or as clinically indicated. Serum transaminases and total bilirubin levels should also be obtained within 1 month following changes in EPIDIOLEX dosage and addition or of changes in medications that are known to impact the liver. Consider more frequent monitoring of serum transaminases and bilirubin in patients who are taking valproate or who have elevated liver enzymes at baseline.

Baseline Transaminase Elevations

![Transaminase Elevations](image)

If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, right upper quadrant abdominal pain, fatigue, anorexia, or jaundice or dark urine), promptly measure serum transaminases and total bilirubin and interrupt treatment if serum transaminase levels of greater than 5 times the ULN are observed. If there are clinical indications, patients with prolonged elevations of serum transaminases should be evaluated for other possible causes.

Consider dosage adjustment of any co-administered medication that is known to affect the liver (e.g., valproate and clobazam).

Somnolence and Sedation - EPIDIOLEX can cause somnolence and sedation. In controlled studies for LGS and DS (10 and 20 mg/kg/day dosages), the incidence of somnolence and sedation (including lethargy) was 32% in EPIDIOLEX-treated patients (27% and 34% of patients taking EPIDIOLEX 10 or 20 mg/kg/day, respectively), compared with 11% in patients on placebo and was generally dose-related. The rate was higher in patients on concomitant clobazam (46% in EPIDIOLEX-treated patients taking clobazam compared with 16% in EPIDIOLEX-treated patients not on clobazam). In the controlled study for TSC, the incidence of somnolence and sedation (including lethargy) was 19% in EPIDIOLEX-treated patients (25 mg/kg/day), compared with 17% in patients on placebo. The rate was higher in patients on concomitant clobazam (33% in EPIDIOLEX-treated patients taking clobazam compared with 14% in EPIDIOLEX-treated patients not on clobazam). In general, these effects were more common early in treatment and may diminish with continued treatment. Other CNS depressants, including alcohol, could potentiate the somnolence and sedation effect of EPIDIOLEX. Prescribers should monitor patients for somnolence and sedation and should advise patients not to drive or operate machinery until they have gained sufficient experience on EPIDIOLEX to gauge whether it adversely affects their ability to drive or operate machinery.

Suicidal Behavior and Ideation - Antiepileptic drugs (AEDs), including EPIDIOLEX, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior. Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27863 AED-treated patients was 0.43%, compared to 0.24% among 16029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the
number is too small to allow any conclusion about drug effect on suicide. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed [see Warnings and Precautions in full P1 for absolute and relative risk by indication for all evaluated AEDs].

The relative risk for suicidal thoughts or behavior was higher in clinical trials in patients with epilepsy than in clinical trials in patients with psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications. Anyone considering prescribing EPIDIOLEX or any other AED must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

**Hypersensitivity Reactions** - EPIDIOLEX can cause hypersensitivity reactions. Some subjects in the EPIDIOLEX clinical trials had pruritus, erythema, and angioedema requiring treatment, including corticosteroids and antihistamines. Patients with known or suspected hypersensitivity to any ingredients of EPIDIOLEX were excluded from the clinical trials. If a patient develops hypersensitivity reactions after treatment with EPIDIOLEX, the drug should be discontinued. EPIDIOLEX is contraindicated in patients with a prior hypersensitivity reaction to cannabidiol or any of the ingredients in the product, which includes sesame seed oil [see Description in full P1].

**Withdrawal of Antiepileptic Drugs (AEDs)** - As with most antiepileptic drugs, EPIDIOLEX should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus [see Dosage and Administration and Clinical Studies in full P1]. But if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered.

**ADVERSE REACTIONS**
The following important adverse reactions are described elsewhere [see Warnings and Precautions in full P1]:
- Hepatocellular Injury
- Somnolence and Sedation
- Suicidal Behavior and Ideation
- Hypersensitivity Reactions
- Withdrawal of Antiepileptic Drugs

**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 practice. In controlled and uncontrolled trials in patients with LGS and DS, 689 patients were treated with EPIDIOLEX, including 533 patients treated for more than 6 months, and 391 patients treated for more than 1 year. In controlled and uncontrolled trials in patients with TSC, 223 patients were treated with EPIDIOLEX, including 151 patients treated for more than 6 months, 88 patients treated for more than 1 year, and 15 patients treated for more than 2 years. In an expanded access program and other compassionate use programs, 271 patients with DS, LGS, or TSC were treated with EPIDIOLEX, including 237 patients treated for more than 6 months, 204 patients treated for more than 1 year, and 140 patients treated for more than 2 years. In placebo controlled trials of patients with LGS or DS (includes Studies 1, 2, 3, and a Phase 2 controlled study in DS), 323 patients received EPIDIOLEX. Adverse reactions are presented below; the duration of treatment in this trial was up to 16 weeks. Approximately 42% of patients were female, 90% were Caucasian, and the mean age was 14 years (range 1 to 57 years). All patients but one (25 mg/kg/day group) were taking other AEDs. In the controlled trial in TSC, the rate of discontinuation as a result of any adverse reaction was 11% for patients taking EPIDIOLEX 25 mg/kg/day and 3% for patients on placebo. The most frequent cause of discontinuation was rash (5%). The most common adverse reactions that occurred in EPIDIOLEX-treated patients with TSC (incidence at least 10% at the recommended dosage and greater than placebo) were diarrhea; transaminase elevations; decreased appetite; somnolence; pyrexia; and

**Adverse Reactions in Patients Treated with EPIDIOLEX in Controlled Trials of LGS and DS (Studies 1, 2, and 3)**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>EPIDIOLEX 10 mg/kg/day</th>
<th>EPIDIOLEX 20 mg/kg/day</th>
<th>Placebo N=75 %</th>
<th>Placebo N=238 %</th>
<th>Placebo N=227 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transaminases elevated</td>
<td>8</td>
<td>16</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>16</td>
<td>22</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>20</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain, discomfort</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>23</td>
<td>25</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue, malaise, asthenia</td>
<td>11</td>
<td>12</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td>4</td>
<td>8</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability, agitation</td>
<td>9</td>
<td>5</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression, anger</td>
<td>3</td>
<td>5</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia, sleep disorder, poor quality sleep</td>
<td>11</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drooling, salivary hypersecretion</td>
<td>1</td>
<td>4</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>3</td>
<td>2</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection, all</td>
<td>41</td>
<td>40</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection, other</td>
<td>25</td>
<td>21</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection, viral</td>
<td>7</td>
<td>11</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection, fungal</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>7</td>
<td>13</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxia, respiratory failure</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In a placebo-controlled trial of patients with TSC (Study 4), 148 patients received EPIDIOLEX. Adverse reactions are presented below; the duration of treatment in this trial was up to 16 weeks. Approximately 42% of patients were female, 90% were Caucasian, and the mean age was 14 years (range 1 to 57 years). All patients but one (25 mg/kg/day group) were taking other AEDs. In the controlled trial in TSC, the rate of discontinuation as a result of any adverse reaction was 11% for patients taking EPIDIOLEX 25 mg/kg/day and 3% for patients on placebo. The most frequent cause of discontinuation was rash (5%). The most common adverse reactions that occurred in EPIDIOLEX-treated patients with TSC (incidence at least 10% at the recommended dosage and greater than placebo) were diarrhea; transaminase elevations; decreased appetite; somnolence; pyrexia; and...
vomiting. The table below lists the adverse reactions that were reported in at least 3% of EPIDIOLEX-treated patients, and at a rate greater than those on placebo, in the placebo-controlled trial in TSC. Adverse reactions were similar in pediatric and adult patients with TSC.

**Adverse Reactions in Patients Treated with EPIDIOLEX in Controlled Trial of TSC (Study 4)**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>EPIDIOLEX</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg/kg/day</td>
<td>N=75</td>
<td>N=76</td>
</tr>
<tr>
<td>Hematological changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Eosinophil count increased</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transaminases elevated</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue, malaise, asthenia</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear infection</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Urinary tract infection</td>
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<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Rash</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Additional Adverse Reactions in Patients with LGS, DS, or TSC

**Decreased Weight** - EPIDIOLEX can cause weight loss. In the controlled trials of patients with LGS or DS (10 and 20 mg/kg/day), based on measured weights, 16% of EPIDIOLEX-treated patients had a decrease in weight of at least 5% from their baseline weight, compared to 8% of patients on placebo. The decrease in weight appeared to be dose-related, with 18% of patients on EPIDIOLEX 20 mg/kg/day experiencing a decrease in weight at least 5%, compared to 9% in patients on EPIDIOLEX 10 mg/kg/day. In the controlled trial of patients with TSC (25 mg/kg/day), 31% of EPIDIOLEX-treated patients had a decrease in weight of at least 5% from their baseline weight, compared to 8% of patients on placebo. In some cases, the decreased weight was reported as an adverse event (see Tables above).

**Hematologic Abnormalities** - EPIDIOLEX can cause decreases in hemoglobin and hematocrit. In controlled trials of patients with LGS or DS, the mean decrease in hemoglobin from baseline to end of treatment was -0.42 g/dL in EPIDIOLEX-treated patients receiving 10 or 20 mg/kg/day and -0.03 g/dL in patients on placebo. A corresponding decrease in hematocrit was also observed, with a mean change of -1.5% in EPIDIOLEX-treated patients and -0.4% in patients on placebo. In the trial of patients with TSC, the mean decrease in hemoglobin from baseline to end of treatment was -0.37 g/dL in EPIDIOLEX-treated patients receiving 25 mg/kg/day and 0.07 g/dL in patients on placebo. A corresponding decrease in hematocrit was also observed, with a mean change of -1.2% in EPIDIOLEX-treated patients and -0.2% in patients on placebo. There was no effect on red blood cell indices. Thirty percent (30%) of EPIDIOLEX-treated patients with LGS and DS and 38% of EPIDIOLEX-treated patients with TSC developed a new laboratory-defined anemia during the course of the study (defined as a normal hemoglobin concentration at baseline, with a reported value less than the lower limit of normal at a subsequent time point), versus 13% of patients with LGS and DS on placebo and 15% of patients with TSC on placebo.

**Increases in Creatinine** - EPIDIOLEX can cause elevations in serum creatinine. The mechanism has not yet been determined. In controlled studies in healthy adults and in patients with LGS, DS, and TSC, an increase in serum creatinine of approximately 10% was observed within 2 weeks of starting EPIDIOLEX. The increase was reversible in healthy adults. Reversibility was not assessed in studies in LGS, DS, or TSC.

**DRUG INTERACTIONS**

**Effect of Other Drugs on EPIDIOLEX**

**Strong CYP3A4 or CYP2C19 Inducers:** Coadministration with a strong CYP3A4 and CYP2C19 inducer (rifampin 600 mg once daily) decreased cannabidiol and 7-OH-CBD plasma concentrations by approximately 32% and 63%. The impact of such changes on efficacy of EPIDIOLEX is not known [see Clinical Pharmacology in full PI]. Consider an increase in EPIDIOLEX dosage (based on clinical response and tolerability) up to 2-fold, when coadministered with a strong CYP3A4 and/or CYP2C19 inducer.

**Effect of EPIDIOLEX on Other Drugs**

**UGT1A8, UGT2B7, CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 Substrates:** In vitro data predict drug-drug interactions with CYP1A2 substrates (e.g., theophylline, caffeine), CYP2B6 substrates (e.g., bupropion, efavirenz), uridine 5'-diphospho-glucuronyltransferase 1A9 (UGT1A9) substrates (e.g., diflunisal, propofol, fenofibrate), and UGT2B7 substrates (e.g., gemfibrozil, lamotrigine, morphine, lorazepam) when coadministered with EPIDIOLEX. Coadministration of EPIDIOLEX is also predicted to cause clinically significant interactions with CYP2C8 and CYP2C9 (e.g., phenytoin) substrates. Because of potential inhibition of enzyme activity, consider a reduction in dosage of substrates of UGT1A9, UGT2B7, CYP2C8, and CYP2C9, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with EPIDIOLEX. Because of potential for both induction and inhibition of enzyme activity, consider adjusting dosage of substrates of CYP1A2 and CYP2B6, as clinically appropriate [see Clinical Pharmacology in full PI].

**Sensitive CYP2C19 Substrates:** In vivo data show that coadministration of EPIDIOLEX increases plasma concentrations of drugs that are metabolized by (i.e., are substrates of) CYP2C19 (e.g., diazepam) and may increase the risk of adverse reactions with these substrates [see Clinical Pharmacology in full PI]. Consider a reduction in dosage of sensitive CYP2C19 substrates, as clinically appropriate, when coadministered with EPIDIOLEX.

**Clobazam:** Coadministration of EPIDIOLEX produces a 3-fold increase in plasma concentrations of N-desmethylclobazam, the active metabolite of clobazam (a substrate of CYP2C19), with no effect on clobazam levels [see Clinical Pharmacology in full PI]. The increase in N-desmethylclobazam may increase the risk of clobazam-related adverse reactions [see Warnings and Precautions in full PI]. Consider a reduction in dosage of clobazam if adverse reactions known to occur with clobazam are experienced when co-administered with EPIDIOLEX.

**Concomitant Use of EPIDIOLEX and Valproate** - Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations [see Warnings and Precautions in full PI]. If such elevations occur, discontinuation or reduction of EPIDIOLEX and/or concomitant valproate should be considered. Insufficient data are available to assess the risk of concomitant administration of other hepatotoxic drugs and EPIDIOLEX.

**Concomitant Use of EPIDIOLEX and Mammalian Target of Rapamycin (mTOR) or Calcineurin Inhibitors** - No dedicated drug-drug interaction studies have been conducted with mTOR inhibitors (e.g., everolimus) or calcineurin inhibitors (e.g., tacrolimus). Reports in the literature suggest that cannabidiol administration resulted in increased serum levels of everolimus, sirolimus, or tacrolimus. The mechanism of increase in mTOR or calcineurin inhibitors concentrations is not clearly understood. Consider a reduction in dosage of everolimus, sirolimus, or tacrolimus, if adverse reactions known to occur with those medications are experienced when co-administered with EPIDIOLEX.
CNS Depressants and Alcohol - Concomitant use of EPIDIOLEX with other CNS depressants (including alcohol) may increase the risk of sedation and somnolence [see Warnings and Precautions in full PI].

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), such as EPIDIOLEX, during pregnancy. Encourage women who are taking EPIDIOLEX during pregnancy to enroll in the North American Antiepileptic Drug (NAED) Pregnancy Registry by calling the toll free number 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org/.

Risk Summary: There are no adequate data on the developmental risks associated with the use of EPIDIOLEX in pregnant women. Administration of cannabidiol to pregnant animals produced evidence of developmental toxicity (increased embryofetal mortality in rats and decreased fetal body weights in rabbits; decreased growth, delayed sexual maturation, long-term neurobehavioral changes, and adverse effects on the reproductive system in rat offspring) at maternal plasma exposures similar to (rabbit) or greater than (rat) that in humans at therapeutic doses (see Animal Data in full PI).

Lactation

Risk Summary: There are no data on the presence of cannabidiol or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for EPIDIOLEX and any potential adverse effects on the breastfed infant from EPIDIOLEX or from the underlying maternal condition.

Pediatric Use - Safety and effectiveness of EPIDIOLEX for the treatment of seizures associated with LGS, DS, or TSC have been established in patients 1 year of age and older. The use of EPIDIOLEX in these indications is supported by adequate and well-controlled studies in patients 2 years of age and older with LGS and DS and in patients 1 year of age and older with TSC. Safety and effectiveness of EPIDIOLEX in pediatric patients below 1 year of age have not been established.

Geriatric Use - Clinical trials of EPIDIOLEX in the treatment of LGS, DS, and TSC did not include a sufficient number of patients aged above 55 years to determine whether or not they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [see Dosage and Administration, Warnings and Precautions, and Clinical Pharmacology in full PI].

Hepatic Impairment - Because of an increase in exposure to EPIDIOLEX, dosage adjustments are necessary in patients with moderate or severe hepatic impairment [see Dosage and Administration, Warnings and Precautions, and Clinical Pharmacology in full PI]. EPIDIOLEX does not require dosage adjustments in patients with mild hepatic impairment.

Please see the full PI for Patient Counseling Information.

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A Team Approach to Asleep Deep Brain Stimulation

Henry Ford Health System’s investment in advanced DBS technology and its commitment to multidisciplinary care has helped them become a leading treatment center for Parkinson disease and related movement disorders.

By: Jason M. Schwalb, MD; Ellen L. Air, MD, PhD; Neepa J. Patel, MD; and Julia A. Wall

TREATMENT OF MOVEMENT DISORDERS, such as Parkinson disease (PD), essential tremor (ET), and dystonia, requires a multidisciplined, patient-focused approach consisting of nonpharmacologic therapy, medications, and surgical treatments or combinations thereof.

Currently, high frequency deep brain stimulation (DBS) is the standard of care when response to medication is inadequate. For PD, the goal of this surgical therapy is to “level out” the patient’s symptom control and help prevent neuronal cell death so they experience fewer fluctuations associated with medications. For ET and dystonia, the benefits of DBS can exceed what patients ever experienced with medication. DBS consists of an implantable neurostimulation system that creates a nondestructive and reversible disruption of the abnormal activity in specific areas of the brain to improve motor symptoms.

The customary method of DBS lead implantation involves the use of preoperative brain images registered in a stereotactic coordinate system and physiological localization using microelectrode-guided mapping of the target regions while patients are awake. Selection of the target is based on disease-specific considerations, including prioritization of the most disabling symptoms. Once implanted, the system is programmed to deliver a low-dose electrical current to the targeted area and disrupt abnormal movements.

Asleep DBS: A Treatment on the Rise

Awake DBS poses challenges for many patients who are claustrophobic, experience severe off-medication symptoms, or have a general fear of being awake and providing critical feedback to the surgeon during the brain surgery. To accommodate patients who have severe reservations to this type of procedure, there is an alternative approach, refined over the last 10 years, called asleep DBS. The asleep version of DBS enables implantation of the leads using real-time computed tomography (CT) or interoperative magnetic resonance imaging (iMRI) guidance rather than the more cumbersome process utilized in awake DBS. Asleep DBS is a real-time, image-guided surgical procedure for placement of electrodes while the patient is under general anesthesia. At Henry Ford Health System (HFHS), the ClearPoint surgical navigation system is used in...
conjunction with iMRI guidance during surgery to ensure accurate placement of the DBS electrodes at the target location. Unlike CT scans or fluoroscopy, iMRI does not involve exposure to radiation, enabling continual magnetic resonance imaging (MRI) scans of the brain throughout the entire procedure to guide the surgery. Clinical outcomes of asleep DBS in patients with PD using the iMRI technique with the ClearPoint system confer at least equal efficacy in comparison to those with frame-based, microelectrode-guided surgery, and with a similar safety profile.7

Establishing a Leading Asleep DBS Program
HFHS was the third facility in the United States to perform iMRI-guided asleep DBS procedures. They recognized an opportunity to excel in their region’s highly competitive neurosurgery market when they established their asleep DBS practice over 10 years ago in Detroit, Michigan. Investing in a state-of-the-art MRI suite connected to an existing operating room, HFHS is now a national leader in brain surgery, garnering referrals from throughout the region and across the United States (FIGURE 1).

FIGURE 1. Image of DBS Suite

This new offering, combined with a strong outreach program, enabled the health system to reach neurologists and patients who previously opted out of awake DBS as a treatment option for PD. In the early stages of the asleep DBS program, education was key. HFHS proactively contacted other regional medical centers, support groups, and the Michigan Parkinson Foundation, to provide presentations, educational materials, and content for newsletters and other communications. These activities helped reach a previously untapped patient cohort and neurologists who could now refer patients to a more comfortable option for DBS surgery.

Today, 80% of the DBS procedures performed at HFHS are conducted while the patient is asleep, and that number continues to rise. Typically, this is the patients’ preference. Throughout the United States, approximately 50 other hospitals perform asleep implantation of DBS. Although the current percentage of asleep iMRI DBS procedures among total DBS procedures is approximately 8%, it has been climbing as more neurologists (and their patients) become educated on the benefits of asleep DBS. Furthermore, many physicians at HFHS attribute much of the dramatic rise in asleep DBS procedures to a relatively novel method of evaluating, preparing, treating, and monitoring patients undergoing asleep DBS.

The Team Approach
A key ingredient to the success of the HFHS asleep DBS program is a multidisciplinary team approach. Recognized as a best practice in academic centers for years, the team approach has permeated into specialties (eg, cardiology, cancer, and diabetes) outside the academic centers over the past 20 years. Health care systems are finding that the team approach is particularly suitable in advanced and aging countries like the United States, where many elderly patients have comorbidities. Accordingly, treatment plans are becoming more technical and complex; they often exceed the abilities of the single physician. The focus of treatment is shifting from disease or disorder management to a more patient-centered, patient-empowered approach, with increasing emphasis on the psychosocial and quality of life-related aspects.12 For health care providers, researchers are finding that working together as a team reduces the number of medical errors, increases patient safety, and can reduce issues that lead to physician fatigue and burnout.13 A typical team for a patient with PD at HFHS might include a neurologist/movement disorder specialist, neuropsychologist, neurosurgeon, coordinator, and other specialists, as required.

The Neurologist
Neurologists, typically movement disorders specialists, play an integral role on the asleep DBS team. They are on the front line and normally the first team member to initiate care for the patient with PD. Depending on the severity or stage of the disease, the neurologist may care for the patient for several years with a regimen of pharmacologic therapies. As the disease progresses, medications may no longer be effective or patients may begin experiencing complications from their treatment, with motor complications becoming a major source of disability.14 At this phase, it is largely the neurologist’s responsibility to identify a patient with PD as a potential candidate for DBS.

Many patients with PD that came to HFHS were previously given the option of awake surgery but often declined it out of fear of being awake during brain surgery, or other factors, such as claustrophobia or severe off-medication symptoms. However, with the advent of asleep DBS, coupled with referring neurologists and patients becoming more educated on the benefits of asleep DBS, patients with PD are reconsidering brain surgery as a realistic option.
Neurologists are also starting to recognize that earlier DBS intervention offers the opportunity to impact patients’ quality of life and functional ability, providing potentially significant symptomatic relief over a longer period. A discernable trend has emerged where patients are pursuing therapy earlier—before they are more severely disabled. The neurologist discusses the patient’s goals for the surgery to establish a patient-centered and symptom-specific outcome for each potential DBS candidate.

The neurologist, who has the relationship and historical knowledge of the patient, is a key contributor in the team decision on whether to move forward with asleep DBS. The neurologist presents potential risks, anticipated adverse effects, and potential electrode target areas based on the current medication regimen and an understanding of the patient’s postoperative goals. He or she remains an active member of the team throughout the entire process, from planning to post-surgery.

At approximately 1-month after surgery, the patient returns to have the system programmed and customized to the patient’s individual indications. The neurologist or movement disorder specialist is typically responsible for programming the device, monitoring the patient and fine tuning as appropriate, but team input is always available. For example, the movement disorder specialist may join the neurologist during the programming sessions and the surgeon might provide images of where the electrodes are placed and remains another resource for the neurologist. Follow-ups for fine-tuning can occur for 3 to 6 months thereafter. Programming can be updated and modified throughout the course of disease progression to optimize therapy.

Coordinator

The focal point of the team concept is the DBS coordinator. The coordinator is the primary contact for the patient and their family/caregiver as they maneuver the entire process, which can be quite daunting within a large hospital. Once the patient decides to undergo asleep DBS, a coordinator is assigned to the case and detailed planning ensues (FIGURE 2). Approximately 50% of the DBS volume at HFHS comes from the internal movement disorders group of specialists. HFHS also has a large neurologist referral network in the community and throughout the region. The coordinator plays a key role collaborating with PD support groups and hosting educational events for referring neurologists and their patients.

Throughout the patient journey, the coordinator manages the schedule, collaborates with team members, and builds a rapport with the patient and their caregivers. He or she schedules preoperative surgical evaluations, confirms that forms are complete and signed, schedules facilities, team meetings, and appointments, and keeps all team members apprised. When possible, patients are scheduled to be seen on the same day for certain procedures, including the levodopa challenge, MRI, and speech evaluation. This process is more time efficient for the patient, engendering improved patient satisfaction. During this phase, the coordinator serves as the primary liaison between the DBS team and the patient. The coordinator ensures that team members have the

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**FIGURE 2. Asleep Deep Brain Stimulation Process Flow Chart**

[Diagram showing the process flowchart for asleep DBS surgery, including key roles and stages such as Referral to HFHS neurology department, Neuropsychological evaluation, Implant IPG, Program for the IPG Based on indications, etc.]
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Neuropsychologist
The neuropsychologist has a vital role in the preoperative screening process because they help distinguish if the patient has PD or a Parkinson-plus syndrome, as the latter tends not to respond to DBS. There is also evidence that patients with significant cognitive disorders are at higher risk of poor outcomes with surgery than medical management. In some cases, the surgery improves their motor symptoms, but it may induce adverse effects such as mood, cognitive, or behavioral problems.14 The neuropsychologist uses preoperative neuropsychological testing to determine risk of major cognitive impairment or dementia and to establish a baseline for later comparison to assess change related to disease progression or surgical factors.

Neuropsychological testing involves an in-depth assessment of skills and abilities linked to brain function, such as attention, problem solving, memory, language, intelligence quotient, visual-spatial skills, academic skills, and social-emotional functioning.17 The neuropsychologist interprets the test results, participates in the multidisciplinary team meetings to discuss the pros and cons for a DBS solution, and provides input on target selection.

Neurosurgeon
Neurosurgeons at HFHS who have been performing asleep DBS for the past decade possess significant, valuable experiences with a variety of PD, ET, and other movement disorders; they assert the team concept as an ideal modus operandi in treating these conditions. Surgeons recognize that the other team specialists approach these situations differently, and at times, identify issues that the rest of the team did not see. Taking a multidisciplinary, 360-degree approach may produce some redundancy, but it also reduces risks and gives the patient (and family) greater confidence knowing that the entire team is focused on their well-being and the best outcome.

The DBS team at HFHS is a close-knit group who physically works in a central location on the same floor. This arrangement fosters informal, enhanced communications outside of the structured patient management communications between the specialists who actively participate in evaluating patients prior to and following surgery. The neurosurgeon, for example, relies heavily on perspectives of the neurologist and neuropsychologist to determine the anatomical target for the electrodes that will result in the best patient outcome.

Employing the ClearPoint system for asleep DBS, HFHS neurosurgeons are routinely expected to achieve submillimetric accuracy in lead placement procedures. To facilitate this accuracy, ClearPoint’s aiming device and software were developed specifically for iMRI interventions. Although the workflow of both awake and asleep DBS is similar, many of the asleep DBS guidance measures are automated, potentially saving time while maintaining flexibility and increased control over the procedure. In addition, the surgeon does not encounter a time limitation when the patient can no longer physically endure the procedure, which can occur during awake DBS. Finally, the asleep procedure eliminates the need for microelectrode or physiologic mapping, reducing brain penetrations and enabling bilateral intraoperative visualization of the subthalamic nucleus (or globus pallidus pars interna) and the DBS electrode simultaneously, detecting potential complications immediately. This technique increases patient comfort by eliminating the need for stereotactic frame or bone fiducials placement and enables the procedure to be done under general anesthesia.18

Following recovery, the patient returns and the neurosurgeon implants an internal pulse generator (IPG) under their respective clavicle and connects the electrical probes. Typically, 1 IPG is used for 2 DBS electrodes.

Clinical and Economic Benefits
Clinically, perhaps the greatest benefit of the team approach is having multiple perspectives in the evaluation, planning, surgery, and aftercare phases. Each discipline imparts a slightly different, yet valuable perspective on how they view the patient’s history, data, clinical evaluations, and goals. This results in improved outcomes for the patient undergoing DBS. Additionally, the adoption of the team approach for DBS could result in fewer errors and readmissions; however, this theory needs to be validated in studies.

The option of asleep DBS can provide a competitive advantage by attracting more patients who may have opted out of the awake DBS surgical procedure. Further, the asleep version combines much of the planning phase with the actual surgery, streamlining the overall process and, according to HFHS neurosurgeons, results in a more focused, less stressful surgery. In addition, the Affordable Care Act and the Centers for Medicare & Medicaid link Medicare reimbursement to patient satisfaction scores.19 With the asleep option gaining favor with many patients, hospitals who offer asleep DBS may benefit from a positive patient experience assessment.

Conclusions
As evidenced at HFHS, the team approach to asleep DBS surgery is a model that is critical to providing the best care for patients and results in optimal patient outcomes. Collaboration from a broad range of related specialists also results in greater patient and clinician satisfaction. The circumstances in any individual hospital will be unique, but the collaborative process described here can help other asleep DBS programs achieve and demonstrate the best outcomes possible.

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

**Muscular Dystrophy Association Awards 5 Grants for ALS Research**
The Muscular Dystrophy Association awarded 5 new grants, totaling more than $1.6 million, toward research efforts focused on amyotrophic lateral sclerosis (ALS). The funding will go to projects that will aim to create a clinical trial platform for testing multiple drugs simultaneously, deploy an ALS toolkit, continue development of a biobank and database that can be used by ALS researchers, and develop and validate a new gene therapy strategy for ALS and frontotemporal degeneration. Additionally, the funding will be used to help prepare for a personalized clinical trial of a novel treatment for ALS symptoms while also supporting research into risk factors and the root cause of ALS. The ALS grant awardees for this cycle are Sabrina Paganoni, MD, PhD; Michael Benatar, MD, PhD; Jonathan Glass, MD; Jeffrey Rothstein, MD, PhD; and Hiroshi Mitsumoto, MD.

**NIH Awards Grant for Neurodegenerative Disease Diagnostic Technology**
CND Life Sciences was awarded a $2.4 million phase 2 Small Business Innovation Research grant from the National Institute of Neurological Disorders and Stroke of the National Institutes of Health to support the continued validation and enhancement of the Syn-One Test, which helps physicians diagnose Parkinson disease and other related disorders. Todd Levine, MD, neuromuscular neurologist and cofounder and chief medical officer at CND, will serve as the principal investigator on the 500-patient, multicenter clinical study. If successful, the large-scale assessment of CND’s diagnostic approach and pathological methods will provide physicians and patients with even greater evidence to support broad clinical adoption of the Syn-One Test. Physicians ordering the Syn-One Test receive a detailed report of the pathologic findings of the test, including visual images of the patient’s cutaneous nerve fibers and a determination of the presence of abnormal synuclein.

**Michael Wilson, MD, Awarded 2020 Trailblazer Prize by NIH**
The Foundation for the National Institutes of Health awarded its annual Trailblazer Prize for Clinician-Scientists to Michael Wilson, MD, for pioneering a next-generation diagnostic approach to pinpoint infectious causes of inflammatory conditions of the central nervous system. The award recognizes early career clinician-scientists whose outstanding research contributions translate to paradigm-shifting approaches for diagnosing, preventing, treating or curing disease and disability. Wilson currently serves as an associate professor of neurology in the Division of Neuroimmunology and Glial Biology at the University of California, San Francisco, Weill Institute for Neurosciences. He employed the innovative technique of metagenomic next-generation sequencing, which analyzes the genetic material in a patient’s sample and precisely identifies specific infectious agents causing inflammation while also ruling out irrelevant pathogens that might otherwise have been suspected. In addition to the award, Wilson was gifted a $10,000 honorarium.

**Feng Guo, PhD, Receives NIH Grant for Autoimmune Disease Research**
The NIH awarded $2.3 million to Feng Guo, PhD, to advance research in autoimmune disease. Guo, an assistant professor of intelligent systems engineering at the Luddy School of Informatics, Computing, and Engineering of Indiana University, was the recipient of the 2020 NIH Director’s New Innovator Award, which is given to investigators who propose innovative, high-impact projects in the biomedical, behavioral, or social sciences. Guo’s research will focus on the diagnosis, prognosis, and treatment of multiple sclerosis, as well as other autoimmune diseases, such as rheumatoid arthritis and Crohn disease. Additionally, he will develop new approaches for measuring cell adhesion, or cell “stickiness,” which can be used as a marker to monitor the progression of many autoimmune and metastatic diseases.

**Three-Year Grant Funds Study on Molecular Aging and Parkinson Disease**
The University of Minnesota Medical School and Van Andel Institute initiated a $6.2 million study that seeks to define the molecular linkages between aging and Parkinson disease (PD). Funding for the study came from a 3-year grant from the Aligning Science Across Parkinson’s initiative, an international collaborative research effort partnering with The Michael J. Fox Foundation for Parkinson’s Research. The study will combine 4 labs, 2 of which will be led by Michael Lee, PhD, professor in the Department of Neuroscience, and Laura Niedernhofer, PhD, professor in the Department of Biochemistry, Molecular Biology, and Biophysics, at the University of Minnesota Medical School. Investigators in the study will investigate genes such as LRRK2, VPS35, and α-synuclein, or SNCA, all of which are associated with late-onset PD, to determine if increased senescence is associated with the disease and whether decreasing senescence can slow or stop the disease.

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61
Discover the History of Monoclonal Antibodies, the Pathophysiology of CGRP in Migraine, and a Therapeutic Option for Migraine Prevention

Join expert faculty in this educational iPub® to learn more about migraine pathophysiology and a therapeutic option for migraine prevention.

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In this iPub®, Drs. Jessica Ailani and Andrew Charles will:

- Provide an overview of migraine pathophysiology, the history and design considerations of therapeutic monoclonal antibodies, and the basis for targeting calcitonin gene-related peptide (CGRP) for the treatment of migraine
- Present the results from clinical trials demonstrating the efficacy and safety of a monoclonal antibody in the preventive treatment of migraine
- Review current recommendations for migraine prevention and examine characteristics for patient selection

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