Less Invasive Epilepsy Surgery May Help Turn Candidates Into Consults

BY ROHINI K. COORG, MD

Preventing Secondary Stroke: Practical Application of Updated Guidelines
BY SANA SOMANI, MD; AND PRACHI MEHNDIRATTA, MBBS, FAHA

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BY JENNIFER S. SUN, PHD
SPINRAZA—Strong history, powerful evidence

SPINRAZA has been studied in infants and children in the longest clinical trial program in SMA to date. SPINRAZA also has the most published real-world evidence in adults up to age 72 with SMA.

Explore the history below.

Individual results may vary based on several factors, including severity of disease, initiation of treatment, and duration of therapy.

SPINRAZA pivotal trials did not include adults with SMA.

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%).

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.
IMPORTANT SAFETY INFORMATION (cont’d)

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 the brief summary of Prescribing Information on the following pages.

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 external 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.

In clinical studies, 346 patients (47% male, 76% Caucasian) were treated with SPINRAZA, including 314 exposed for at least 6 months, 258 exposed for at least 1 year, and 138 exposed for at least 2 years. 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; in a sham-controlled trial in 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=84 for SPINRAZA, n=42 for control); an open-label study in presymptomatic infants (Study 3, n=25) and other studies in symptomatic infants (n=54) and later-onset patients (n=103). 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 (89% vs 66%), pneumonia or respiratory symptoms (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 (Study 1)

<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 influenza, 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 mg(^1) 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 294 patients with post-baseline plasma samples evaluated for anti-drug antibodies (ADAs). Seventeen patients (6%) developed treatment-emergent ADAs, of which 5 were transient, 12 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.

**6.3 Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of SPINRAZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serious infections associated with lumbar puncture, such as meningitis, have been observed. Hydrocephalus, aseptic meningitis, and hypersensitivity reactions (e.g. angioedema, urticaria, rash) have also been reported.
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. Nusinersen was detected in the milk of lactating mice when administered by subcutaneous injection. 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)].

Manufactured for:
Biogen
Cambridge, MA 02142
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Less Invasive Epilepsy Surgery May Help Turn Candidates Into Consults

BY ROHINI K. COORG, MD

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Questions Linger Around COVID-19’s Origin

**WAS IT NATURAL ZOONOTIC SPILLOVER** that catapulted SARS-CoV-2 from an emerging virus into a pandemic pathogen, or was it something much more sinister? Is it at all possible that a lab leak in Wuhan, China, was the spark that lit the fuse?

Debate and discussion about the origin of the virus that causes COVID-19 have been at the forefront of the global consciousness since the first cases were reported in December 2019. Early on, whispers of a potentially engineered virus quickly grew to a roar and fueled speculation that China was behind the pandemic. This narrative was so pervasive that, in February 2020, a group of 27 public health scientists published a letter in *The Lancet* disputing the lab leak theory and announcing their support of their counterparts in China: the scientists, public health officials, and medical professionals combating the pandemic.

“The rapid, open, and transparent sharing of data on this outbreak is now being threatened by rumors and misinformation around its origins,” wrote the authors, who all declared no competing interests in their disclosures as recommended by the International Committee of Medical Journal Editors. “We stand together to strongly condemn conspiracy theories suggesting that COVID-19 does not have a natural origin.”

And although it’s true that analyses of the genomic sequence of the virus subsequently pointed to natural origins, the questions regarding China’s role persisted, led by pesky discrepancies and conflicting reports.

Fast-forward to June 2021 and new evidence that has breathed new life into those origin questions. In an update to the February 2020 letter, *The Lancet* has published an addendum with revised disclosure statements from virologist and investigator Peter Daszak, 1 of the 27 authors. In the revised document, Daszak noted that his remuneration is paid solely in the form of a salary from EcoHealth Alliance, a New York–based nonprofit research foundation of which he is president. The company has reportedly worked directly with Wuhan laboratories and funded gain-of-function research at China’s Wuhan Institute of Virology.

Consider, too, other odd associations. Recent reports have uncovered financial ties between Google and EcoHealth Alliance. This comes after accusations that the tech giant was censoring lab leak “conspiracy theory” stories in its search results. Google’s health lead, David Feinberg, has dismissed those reports, insisting that the company is simply taking steps to protect users from unverified information.

Are these coincidences or “where there’s smoke, there’s fire” situations? It’s unclear. But they add to the bank of troublesome questions standing in the way of the truth about COVID-19.

The questions extend beyond origin theory, though. With the FDA’s green lighting of vaccines for adolescents and young adults comes hesitation over long-term effects: What is the effect on fertility? Do the vaccines cause heart inflammation? Robert Malone, MD, the inventor of the messenger RNA (mRNA) technology, appeared on television recently, expressing strong concern over the risk-benefit analysis of vaccination for young adults, and the CDC’s Advisory Committee on Immunization Practices recently met to discuss instances of myocarditis or pericarditis in people 30 years and younger who have received an mRNA COVID-19 vaccine.

Of course, the answer to our ultimate question is that we may never know. We may never know where this virus came from. We may never know what triggered the global pandemic that has claimed more than 4.2 million lives. And we won’t know the long-term effects until enough time has elapsed. What we do know for certain is that the incredible strength and collaboration of the scientific community have allowed us to regain some semblance of normalcy. The development and rollout of multiple effective vaccine options have been the medical miracle of our lifetime.

That, right now, will have to be the only answer that matters. ■

Thank you for reading.

Mike Hennessy Sr
Chairman and Founder, MJH Life Sciences™
It Is Time to Redefine Outcomes in Pediatric Epilepsy Surgery

By Jurriaan Peters, MD, PhD

EPILEPSY SURGERY, LIKE ALL MAJOR clinical interventions, took a foothold in adults before its application in pediatrics. Highly functioning adults undergo a standard anterior temporal lobectomy in the context of a clearly defined goal of seizure freedom. The success rate of temporal lobe resections is approximately 60% to 80%.1

The current Engel Outcome Scale, in particular for retrospective studies, captures the epilepsy aspects of surgical outcomes well.2 But then came other byproducts of successful epilepsy surgery in adults: forced normalization, depression, and memory issues.

Thus, the outcome metrics are not suited for the study of broader outcomes—and this problem is more prominent in pediatric epilepsy surgery.

Neuropsychological evaluations can be considered the “gold standard” of qualification and, with standardized tests, quantification of how a person is functioning in life. Freedom from seizures is meaningless if one cannot partake in essential aspects of life in an increasingly interconnected society. Socioeconomic success, freedom from mental health, and long-lasting relationships are not captured by a seizure outcome scale. Even additional metrics like memory function, and verbal and nonverbal IQ are insufficient when not placed in a bigger societal context. According to Martin Buber, interactioning with others is what defines the human experience.3

For research purposes, however, in the investigation of optimal timing, presurgical work-up, surgical technique, and other factors that drive surgical success, key neurodevelopmental aspects will need to be quantified. Bradley Schlaggar, MD, PhD, president and CEO, Kennedy Krieger Institute, posed during the 2016 Annual Flux Congress that in the study of interventions aimed at improving neurodevelopmental outcomes, investigators should not only rely on established clinical neuropsychological measures, but also to engage cognitive neuroscientists in the trial design. Poorly chosen outcome measures can blow a hole in a clinical trial.

Indeed, several barriers exist that prevent the use of standard neuropsychological test batteries in longitudinal assessment of overall neurological outcome in epilepsy surgery.4 First, there is an abundance of confounders and covariates, including but not limited to parental intelligence, socioeconomic status, and complex psychoactive and antiepileptic drug regimens. There can be comorbid neurodevelopmental conditions, such as autism spectrum disorder, that limit cooperation and underestimate abilities. Second, the majority of tests are neither design nor validated for serial use—in younger children test scores may allow for reliance on caregiver report, with possible overestimation of abilities. The wide age range, the steep developmental trajectories, and the variation in the neurological phenotype prevent the use of a single battery of tests across all patients. The domain-specific subscores are converted to composite scores, which can be negatively affected by 1 disproportionately poorly scored item, eg, a postsurgical motor deficit. Use of age-equivalent scores for each subtest can only partially address this issue.4

In children, the strengths and weaknesses in the neurodevelopmental profile determine educational achievement, and are highly predictive of later socioeconomic functioning in life. Performed during steep and thus critical phases of neurodevelopment, early epilepsy surgery yields a larger developmental bang for one’s buck.3,5,6 Moreover, even an incomplete surgical success such as an Engel Epilepsy Surgery Outcome Scale Class III score (“worthwhile improvement”) may still yield developmental benefits. In multilesional epilepsy, similar to tuberous sclerosis complex (TSC), when the most critical and threatening seizure type is targeted successfully with surgery, the patient still can have other, milder seizure types.7 The current outcome scales would consider this a failure, but do not consider the improvement in quality of life for the patient and family. Finally, even when relapse of seizures looms after surgery, a period of seizure freedom can result in marked and sustained...
developmental gains. With stereoelectroencephalography and magnetic resonance thermography–guided laser interstitial thermal therapy, for some children repeated smaller surgeries could be more beneficial than a "one-and-done" large open resection while setting unrealistic expectations of permanent seizure freedom.

On a pathophysiological level, the detrimental effects of recurrent seizures on the developing brain are evident on serial encephalography (EEG). Because of use-dependent plasticity, a primary mechanism of learning in the human brain, seizures evolve from focal to regional and ultimately to rapidly spreading global seizures. Intercitial focal spikes may similarly develop into a pattern of a widespread epileptic encephalopathy. In TSC, serial EEGs demonstrated such focal spikes precede seizure onset, and over time increased network connectivity precedes generalized seizures. At that time, seizures like epileptic spasms and tonic seizures may no longer localize, and thus surgical interventions may be limited in scope.

In summary, although the developmental benefits follow the surgical reduction of the seizure burden, the current outcome metrics do not capture the broader goals of epilepsy surgery. Such goals include optimizing neurodevelopment, preventing the epileptic encephalopathy, and improving the quality of life for our patients and families.

REFERENCES
Acting FDA Commissioner Calls for Independent Review of Agency Interactions on Aducanumab

By Matt Hoffman

The acting commissioner of the FDA, Janet Woodcock, MD, announced in early July that she is requesting an independent review and assessment of the interactions between representatives of Biogen and the agency during the process that led to the approval of the company’s controversial Alzheimer disease treatment, aducanumab (Aduhelm). The Office of the Inspector General of the Department of Health and Human Services will conduct the review, which it aims to complete in the fiscal year 2023.1

“We believe an independent assessment is the best manner in which to determine whether any interactions that occurred between the manufacturer and the agency’s review staff were inconsistent with FDA’s policies and procedures. We believe this review and assessment will help ensure continued confidence in the integrity of FDA’s regulatory processes and decision-making,” Woodcock wrote in a thread of tweets on her Twitter account.

Her letter to the inspector general noted the significant attention and controversy that have followed this agent since Biogen’s 2019 about-face of its submission to the agency after discontinuing the 2 pivotal phase 3 trials, EMERGE (NCT02484547) and ENGAGE (NCT02477800), as well as a phase 2 safety study, EVOLVE (NCT03639987). Woodcock also noted that she has “tremendous confidence in the integrity” of the agency’s staff and leadership at the Center for Drug Evaluation and Research and their need to remain unbiased in their decision-making.

However, she noted the contact between aducanumab’s developer, Biogen, and the agency during the process of the review, some of which, she wrote, “may have occurred outside of the formal correspondence process.” Because these concerns could “undermine the public’s confidence” in the decision to approve aducanumab, she wrote that conducting an investigation into any potential interactions that were inconsistent with FDA policy and procedure is essential.

The request for inquiry appears to stem in part from reporting from *Stat* in June, which noted that an informal meeting took place in May 2019 between Alfred Sandrock Jr, MD, PhD, head of research and development, Biogen, and Billy Dunn, MD, deputy director, FDA Neuroscience Office, at a conference in Philadelphia, Pennsylvania.3

“If the Office of the Inspector General decides to conduct the review, the agency will fully cooperate, [and] should they provide the agency with any recommendations, FDA would review expeditiously to determine the best course of action,” Woodcock tweeted, closing the thread with “The trust of the American public, especially during these difficult times[,] is of the utmost importance to the FDA—and we will continue to exercise transparency around our decision-making as allowed by the law.”

Many have called into question the FDA’s decision to approve the Biogen agent, with much of the concern focused on the complicated and complex nature of both the submission process for the drug, the accelerated approval pathway that was utilized to OK the drug, and its potential clinical benefit for patients. After Biogen’s decision to reverse course and submit the agent, the company presented data at the 12th Clinical Trials on Alzheimer’s Disease conference, December 4 to 7, 2019, in San Diego, California, that included an analysis from EMERGE, and a post hoc analysis of a subset of patients who received high-dose treatment in ENGAGE was also presented, suggesting that there were statistically significant changes in the Clinical Dementia Rating Sum of Boxes scores, with *P* values of .010 or .031 based on cutoff dates.

Additionally, the FDA’s own advisory committee, which convened to review the data in November 2020, recommended not to approve aducanumab, and since the approval, a number of members of that Peripheral and Central Nervous System Drugs Advisory Committee have resigned from their positions.

This news came just days after the FDA announced an updated label for the antiamyloid therapy, which included updates to the Indications and Usage section of the 100-mg/mL injection’s label. That updated language states that treatment with aducanumab should be initiated in patients with mild cognitive impairment or mild dementia stages of the disease, the population in which the treatment was initiated in clinical trials. It continues to state that there are no safety or efficacy data on initiating treatment at earlier or later stages of the disease other than what were studied.3

This followed an updated review from the Institute for Clinical and Economic Review (ICER), which suggested that Biogen must drastically reduce the price of its newly approved antiamyloid agent for the therapy to be considered cost-effective for patients. The current list price of aducanumab has been set at $56,000 annually.3 ICER’s new report affirmed its prior publication in May, which suggested that for the agent to be cost-effective, its price would need to be between $2500 and $8300 per patient per year. When calculating the price based on assumed “optimistic” treatment benefits—relying only on the results of the positive study—the price would need to be between $11,100 and $23,100 for it to be considered cost-effective. Based on an assumption of “conservative” treatment benefits, the cost-effective range was reduced to between $1200 and $4200.3

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

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**JOURNAL ROUNDUP**

**North America, Europe Align on New Recommendations for MRI in Multiple Sclerosis**

By Alicia Bigica

For the first time, experts in multiple sclerosis (MS) from North America and Europe have aligned on consensus recommendations for the use of MRI in individuals with MS. These guidelines—developed by the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) study group, the Consortium of Multiple Sclerosis Centers (CMSC) working group, and the North America Imaging in Multiple Sclerosis Cooperative MRI Guidelines working group—address recent advancements in imaging technology and new safety data, among other clinical updates.

A main focus and key update included in the recommendations is the use of standardized MRI protocols for both diagnostic and...
prognostic purposes, the importance of which was emphasized in the 2017 updates to the McDonald criteria. Previous guidelines from MAGNIMS and CMSC issued in 2015 and 2016, respectively, recommended the use of axial single T2-weighted sequences, dual echo T2-weighted spin echo sequences, axial and sagittal T2-weighted fluid-attenuated inversion recovery (FLAIR), and contrast enhanced axial T1-weighted sequences, preferably at 3 Tesla (T). Although these recommendations are still in line with the current McDonald criteria, the new recommendations emphasize the use of 3D acquisition techniques, especially for FLAIR and T1-weighted sequences, as they can both improve lesion detection and contribute to better realignment of anatomic orientation on serial scans.

The groups recommend sagittal 3D FLAIR acquisition as the core sequence used for both diagnosis and monitoring of MS, but high-quality 2D pulse sequences, with less than or equal to 3-mm slice thickness and no gap between slices, are an acceptable alternative. Although 3T scanners offer optimal lesion detection and acquisition times, 1.5T scanners are sufficient; those with a strength of less than 1.5T are not recommended. Notably, the groups do not recommend the use of 7T scanners at this time, reserving their use for research purposes.

Pointing out the high value of spinal cord MRI to show dissemination in time and space and for exclusion of other diagnoses, the groups recommend that the standard MS imaging protocol include at least 2 of the following 3 sagittal sequences: T2-weighted spin echo with moderately long echo times, proton density-weighted echo, and short tau inversion recovery. If contrast agents are used, a T1-weighted spin echo sequence should be included as well.

In light of new safety advisories from both the FDA and the European Medicines Agency regarding the accumulation of gadolinium-based contrast agents (GBCAs) in the brain, the recommendations support the continued use of single-dose GBCA—but not double- or triple-dose—with special considerations for time delay between GBCA administration and T1-weighted acquisition (ideally 10 minutes) during initial and subsequent scans.

Emerging Biomarkers
Several new imaging biomarkers of MS, most notably the central vein sign, have begun to emerge in the literature. Although valuable for distinguishing MS from mimics, central vein sign in routine clinical use is not currently recommended by the groups, as the pulse sequences needed for detection are not widely available on clinical scanners and expert image interpretation is required. Similarly, paramagnetic rim lesions and leptomeningeal inflammation are not currently recommended, because more time is needed to validate these as imaging biomarkers.

MRI for Treatment Effectiveness and Disease Monitoring
After a baseline MRI (with or without GBCA), the groups recommend a new brain MRI without GBCAs 3 to 6 months after starting treatment or switching their disease-modifying therapy (DMT). Annual brain MRI should continue while on DMT, and longer intervals are acceptable for those who are clinically stable or do not require safety monitoring after several years of treatment. Brain MRI should be performed in an identical manner at each follow-up according to the previously mentioned protocol, whereas spinal cord and optic nerve MRI are not routinely recommended unless clinical situations require them. New or enlarging T2 lesions should be reported, as well as recognition of poor sensitivity for cortical gray matter lesions and use of coregistration, fusion, and subtraction tool techniques. Notably, volumetric and quantitative MRI measures are not routinely recommended.

MRI Use in Other Populations
The consensus guidelines have also been applied across other patient populations, including pediatric patients and women with MS who are pregnant or in the postpartum period. For pediatric patients, the same standardized brain and spinal cord MRI protocols and follow-up scan frequency used in adults should be applied. If MRI is necessary during pregnancy, (ie, unexpected disease activity or comorbidity), standard protocols should be applied using 1.5T, with no use of GBCAs. In the postpartum period, MRI acquisition can be done under normal standardized protocols, but GBCAs should be used only if highly necessary and the patient is lactating. Notably, the guidelines recommend a new baseline MRI 2 to 3 months postpartum.

Overall, the guidelines reflect a movement toward more consistent and purposeful patient evaluation that takes into account the varying degrees of available imaging technology and software, time limitations, and interpretation expertise. With a goal of global adoption and standardization, these guidelines truly serve as a consensus and reflect the latest verified clinical techniques for diagnosing and monitoring MS.

“The CMSC is extremely proud to be a partner in the development and endorsement of international recommendations for MRI in multiple sclerosis,” CMSC CEO June Halper told NeurologyLive®. “The standards recommended in this paper will further enhance the expert MS care provided to patients worldwide.”

REFERENCE

To see what’s streaming live on Medical World News, head to www.medicalworldnews.com, or scan the QR code.
ONPATTRO® (patisiran) can reverse polyneuropathy manifestations of the disease \(^4\)

A novel RNAi-based approach that may transform the future for your patients \(^1,4-6\)

Patients and their families face a future of functional decline \(^1-3\)

**Important Safety Information**

**Infusion-Related Reactions (IRRs)**

In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. The most common symptoms of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache.

To reduce the risk of IRRs, patients should receive premedication with a corticosteroid, acetaminophen, and antihistamines (H\(_1\) and H\(_2\) blockers) at least 60 minutes prior to ONPATTRO infusion. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the infusion. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

**Reduced Serum Vitamin A Levels and Recommended Supplementation**

ONPATTRO treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance (RDA) of vitamin A is advised for patients taking ONPATTRO.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

**Adverse Reactions**

The most common adverse reactions that occurred in patients treated with ONPATTRO were upper respiratory tract infections (29%) and infusion-related reactions (19%).

Please see brief summary of full Prescribing Information following this ad.

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**References:**

ONPATTRO® (patisiran) can reverse polyneuropathy manifestations of the disease\textsuperscript{4}

A novel RNAi-based approach that may transform the future for your patients\textsuperscript{1,4-6}

ONPATTRO is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Study Design
The efficacy of ONPATTRO was demonstrated in a randomized, double-blind, placebo-controlled, multicenter clinical trial in adults with hATTR amyloidosis with polyneuropathy. Patients were randomized to receive ONPATTRO 0.3 mg/kg (N=148) or placebo (N=77) via intravenous infusion once every 3 weeks for 18 months.

Primary endpoint: The modified Neuropathy Impairment Score + 7 (mNIS+7) is an objective 304-point assessment of neuropathy that measures cranial nerve function, muscle strength, reflexes, postural blood pressure, quantitative sensory testing, and peripheral nerve electrophysiology.

Key secondary endpoint: The Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) scale is a patient-reported assessment that evaluates neuropathy in the following domains: physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy (score range -4 to 136).

Select secondary endpoint: The Composite Autonomic Symptom Score 31 (COMPASS 31) is a patient-reported questionnaire that evaluates 6 autonomic domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor (score range 0 to 100).

At 18 months, ONPATTRO demonstrated:

- **Reversal in neuropathy impairment**\textsuperscript{4}
  - Mean change from baseline in mNIS+7 of -6.0 points vs 28.0 with placebo, a treatment difference of -34 points (95% CI: -39.9, -28.1; p<0.001)

- **Improvement in quality of life**\textsuperscript{4}
  - Mean change from baseline in Norfolk QoL-DN score of -6.7 points vs 14.4 with placebo, a treatment difference of -21.1 points (95% CI: -27.2, -15.0; p<0.001)

- **Reduction in autonomic symptoms**\textsuperscript{6,7}
  - Mean change from baseline in COMPASS 31 of -5.3 points vs 2.2 with placebo, a treatment difference of -7.5 points (95% CI: -11.9, -3.2; p<0.001)

CI=confidence interval; RNAi=ribonucleic acid interference.

Visit www.onpattrohcp.com to get your patients started.
ONPATTRO® (patisiran) lipid complex injection, for intravenous use

Initial U.S. Approval: 2018

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

ONPATTRO is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

DOSAGE AND ADMINISTRATION

Dosing Information

ONPATTRO should be administered by a healthcare professional. ONPATTRO is administered via intravenous (IV) infusion. Dosing is based on actual body weight. For patients weighing less than 100 kg, the recommended dosage is 0.3 mg/kg once every 3 weeks. For patients weighing 100 kg or more, the recommended dosage is 30 mg once every 3 weeks.

Missed Dose

If a dose is missed, administer ONPATTRO as soon as possible. If ONPATTRO is administered within 3 days of the missed dose, continue dosing according to the patient’s original schedule. If ONPATTRO is administered more than 3 days after the missed dose, continue dosing every 3 weeks thereafter.

Required Premedication

All patients should receive premedication prior to ONPATTRO administration to reduce the risk of infusion-related reactions (IRRs) [see Warnings and Precautions (5.1) in the full Prescribing Information]. Each of the following premedications should be given on the day of ONPATTRO infusion at least 60 minutes prior to the start of infusion: intravenous corticosteroid (e.g., dexamethasone 10 mg, or equivalent); oral acetaminophen (500 mg); intravenous H1 blocker (e.g., diphenhydramine 50 mg, or equivalent); and intravenous H2 blocker (e.g., ranitidine 50 mg, or equivalent).

For premedications not available or not tolerated intravenously, equivalents may be administered orally.

For patients who are tolerating their ONPATTRO infusions but experiencing adverse reactions related to the corticosteroid premedication, the corticosteroid may be reduced by 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (intravenous), or equivalent.

Some patients may require additional or higher doses of one or more of the premedications to reduce the risk of IRRs [see Warnings and Precautions (5.1) in the full Prescribing Information].

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. In clinical studies, all patients received premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) to reduce the risk of IRRs. In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. Among ONPATTRO-treated patients who experienced an IRR, 79% experienced the first IRR within the first 2 infusions. The frequency of IRRs decreased over time. IRRs led to infusion interruption in 5% of patients. IRRs resulted in permanent discontinuation of ONPATTRO in less than 1% of patients in clinical studies. Across clinical studies, the most common symptoms (reported in greater than 2% of patients) of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache [see Adverse Reactions (6.1) in the full Prescribing Information]. One patient in the ONPATTRO expanded access program had a severe adverse reaction of hypotension and syncope during an ONPATTRO infusion.

Patients should receive premedications on the day of ONPATTRO infusion, at least 60 minutes prior to the start of infusion [see Dosage and Administration (2.2) in the full Prescribing Information]. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the ONPATTRO infusion and instituting medical management (e.g., corticosteroids or other symptomatic treatment), as clinically indicated. If the infusion is interrupted, consider resuming at a slower infusion rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

Some patients who experience IRRs may benefit from a slower infusion rate or additional or higher doses of one or more of the premedications with subsequent infusions to reduce the risk of IRRs [see Dosage and Administration (2.2) in the full Prescribing Information].

Reduced Serum Vitamin A Levels and Recommended Supplementation

ONPATTRO treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A is advised for patients taking ONPATTRO. Higher doses than the recommended daily allowance of vitamin A should not be given to try to achieve normal serum vitamin A levels during treatment with ONPATTRO, as serum vitamin A levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

ADVERSE REACTIONS

Clinical Trials Experience

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

A total of 224 patients with polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) received ONPATTRO in the placebo-controlled and open-label clinical studies, including 186 patients exposed for at least 1 year. 137 patients exposed for at least 2 years, and 52 patients exposed for at least 3 years. In the placebo-controlled study, 148 patients received ONPATTRO for up to 18 months (mean exposure 17.7 months).

Upper respiratory tract infections and infusion-related reactions were the most common adverse reactions. One patient (0.7%) discontinued ONPATTRO because of an infusion-related reaction.

Table 1 lists the adverse reactions that occurred in at least 5% of patients in the ONPATTRO-treated group and that occurred at least 3% more frequently than in the placebo-treated group in the randomized controlled clinical trial.

Table 1: Adverse Reactions from the Placebo-Controlled Trial that Occurred in at Least 5% of ONPATTRO-Treated Patients and At Least 3% More Frequently than in Placebo-Treated Patients

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ONPATTRO N=148</th>
<th>Placebo N=77</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infections a</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>Infusion-related reaction b</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Dyspnea c d</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms c</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia c</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Erythema c</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Bronchitis c</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Vertigo</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

a Includes nasopharyngitis, upper respiratory tract infection, respiratory tract infection, rhinitis, rhinitis, sinusitis, viral upper respiratory tract infection, upper respiratory tract congestion.

b Includes infusion-related reaction symptoms include, but are not limited to: arthralgia or pain (including back, neck, or musculoskeletal pain), flushing (including erythema of face or skin warm), nausea, abdominal pain, dyspnea or cough, chest discomfort or chest pain, headache, rash, chills, dizziness, fatigue, increased heart rate or palpitations, hypotension, hypertension, facial edema.

c Not part of an infusion-related reaction.

d Includes dyspnea and exertional dyspnea.

Includes bronchitis, bronchitis, bronchitis viral, lower respiratory tract infection, lung infection.

Four serious adverse reactions of atrioventricular (AV) heart block (2.7%) occurred in ONPATTRO-treated patients, including 3 cases of complete AV block. No serious adverse reactions of AV block were reported in placebo-treated patients.

Ocular adverse reactions that occurred in 5% or less of ONPATTRO-treated patients in the controlled clinical trial, but in at least 2% of ONPATTRO-treated patients, and more frequently than on placebo, include dry eye (5% vs. 3%), blurred vision (5% vs. 3%), and vitreous floaters (2% vs. 1%).

Extravasation was observed in less than 0.5% of infusions in clinical studies, including cases that were reported as serious. Signs and symptoms included phlebitis or thrombophlebitis, infusion or injection site swelling, dermatitis (subcutaneous inflammation), cellulitis, erythema or injection site redness, burning sensation, or injection site pain.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to
ONPATTRO® (patisiran) lipid complex injection, for intravenous use

ONPATTRO during pregnancy. Physicians are encouraged to enroll pregnant patients, or pregnant women may register themselves in the program by calling 1-877-256-9526 or by contacting alnymarpregnancyprogram@iqvia.com.

Risk Summary
There are no available data on ONPATTRO use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. ONPATTRO treatment leads to a decrease in serum vitamin A levels, and vitamin A supplementation is advised for patients taking ONPATTRO. Vitamin A is essential for normal embryofetal development; however, excessive levels of vitamin A are associated with adverse developmental effects. The effects on the fetus of a reduction in maternal serum TTR caused by ONPATTRO and of vitamin A supplementation are unknown [see Clinical Pharmacology (12.2), Warnings and Precautions (5.2) in the full Prescribing Information].

In animal studies, intravenous administration of patisiran lipid complex (patisiran-LC) to pregnant rabbits resulted in developmental toxicity (embryofetal mortality and reduced fetal body weight) at doses that were also associated with maternal toxicity. No adverse developmental effects were observed when patisiran-LC or a rodent-specific (pharmacologically active) surrogate were administered to pregnant rats (see Data in the full Prescribing Information).

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
Intravenous administration of patisiran-LC (0, 0.15, 0.50, or 15 mg/kg) or a rodent-specific (pharmacologically active) surrogate (15 mg/kg) to female rats every week for two weeks prior to mating and continuing throughout organogenesis resulted in no adverse effects on fertility or embryofetal development.

Intravenous administration of patisiran-LC (0, 0.1, 0.3, or 0.6 mg/kg) to pregnant rabbits every week during the period of organogenesis produced no adverse effects on embryofetal development. In a separate study, patisiran-LC (0, 0.3, 1, or 2 mg/kg), administered to pregnant rabbits every week during the period of organogenesis, resulted in embryofetal mortality and reduced fetal body weight at the mid and high doses, which were associated with maternal toxicity.

Intravenous administration of patisiran-LC (0, 0.15, 0.50, or 15 mg/kg) or a rodent-specific surrogate (15 mg/kg) to pregnant rats every week throughout pregnancy and lactation resulted in no adverse developmental effects on the offspring.

Lactation
Risk Summary
There is no information regarding the presence of ONPATTRO 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 ONPATTRO and any potential adverse effects on the breastfed infant from ONPATTRO or from the underlying maternal condition.

In lactating rats, patisiran was not detected in milk; however, the lipid components (DLin-MC3-DMA and PEG2000-C-DMG) were present in milk.

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

Geriatric Use
No dose adjustment is required in patients ≥65 years old [see Clinical Pharmacology (12.3) in the full Prescribing Information]. A total of 62 patients ≥65 years of age, including 9 patients ≥75 years of age, received ONPATTRO in the placebo-controlled study. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment
No dose adjustment is necessary in patients with mild hepatic impairment (bilirubin ≤1 x ULN and AST >1 x ULN, or bilirubin >1.0 to 1.5 x ULN) [see Clinical Pharmacology (12.3) in the full Prescribing Information]. ONPATTRO has not been studied in patients with moderate or severe hepatic impairment.

Renal Impairment
No dose adjustment is necessary in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <90 mL/ min/1.73m2) [see Clinical Pharmacology (12.3) in the full Prescribing Information]. ONPATTRO has not been studied in patients with severe renal impairment or end-stage renal disease.

PATIENT COUNSELING INFORMATION

Infusion-Related Reactions
Inform patients about the signs and symptoms of infusion-related reactions (e.g., flushing, dyspnea, chest pain, rash, increased heart rate, facial edema). Advise patients to contact their healthcare provider immediately if they experience signs and symptoms of infusion-related reactions [see Warnings and Precautions (5.1) in the full Prescribing Information].

Recommended Vitamin A Supplementation
Inform patients that ONPATTRO treatment leads to a decrease in vitamin A levels measured in the serum. Instruct patients to take the recommended daily allowance of vitamin A. Advise patients to contact their healthcare provider if they experience ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness) and refer them to an ophthalmologist if they develop these symptoms [see Warnings and Precautions (5.2) in the full Prescribing Information].

Pregnancy
Instruct patients that if they are pregnant or plan to become pregnant while taking ONPATTRO they should inform their healthcare provider. Advise female patients of childbearing potential of the potential risk to the fetus. Encourage patients to enroll in the ONPATTRO pregnancy exposure registry if they become pregnant while taking ONPATTRO [see Use in Specific Populations (8.1) in the full Prescribing Information].

Manufactured for: Alnylam Pharmaceuticals, Inc.
300 Third Street, Cambridge, MA 02142
By: Ajinomoto Althea, Inc.
11040 Roselle Street, San Diego, CA 92121

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INTEGRATING ADVANCED PRACTICE CLINICIANS INTO NEUROLOGY

Calli L. Cook, DNP, APRN, FNP-C, nurse practitioner, Nell Hodgson Woodruff School of Nursing, Emory University, detailed why a cultural shift is needed to incorporate advanced practice clinicians into the neurology space and improve multidisciplinary care.

INP104’S ADVANTAGES AND SAFETY PROFILE IN MIGRAINE

Sheena K. Aurora, MD, vice president of medical affairs in migraine, Impel, discussed findings from the STOP 301 trial of intranasal dihydroergotamine and how the safety profile offers an advantage for patients who would use the agent on-demand.

A CONTROVERSIAL FDA DECISION

A number of health care leaders in the Alzheimer disease space, including neurologists, psychiatrists, geriatricians, and advocacy partners, share their opinions and outstanding questions on the FDA approval and implementation of aducanumab (Aduhelm; Biogen) for the treatment of Alzheimer disease.

IMAGING MS: UPDATED MRI GUIDANCE

Scott D. Newsome, DO, MScS, president, Consortium of Multiple Sclerosis Centers, and David Li, MD, FRCP, director, Multiple Sclerosis/Magnetic Resonance Imaging Research Group, University of British Columbia, discuss new consensus recommendations for the use of MRI in patients with multiple sclerosis.

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- The Ever-Expanding Multiple Sclerosis Therapeutics Landscape
- Multiple Sclerosis Care During a Pandemic
- The Evolving Rehabilitation Strategies for Multiple Sclerosis

**MODERATED BY:**

Ahmed Obeidat, MD, PhD

**FEATURING:**

Hesham Abboud MD, PhD  
Francois Bethoux, MD  
Anne H. Cross, MD  
S. Mitchell Freedman, MD, FAAN  
Gloria von Geldern, MD  
Nicholas C. Ketchum, MD  
Suma Shah, MD  
Rana K. Zabed, MD, FAAN

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Novel Agents Are Equally Safe and Effective for Acute Migraine Treatment

By Victoria Johnson

DATA FROM A RECENT STUDY presented at the 2021 American Headache Society 63rd Virtual Annual Scientific Meeting, held June 3 to 6, suggest that rimegepant (Nurtec ODT; Biohaven), ubrogepant (Ubrelvy; AbbVie), and lasmiditan (Reyvow; Eli Lilly and Company) are all effective in treating acute migraine compared with placebo, with acceptable safety profiles.

These findings were presented by Karissa Johnston, PhD, MSc, principal and scientific director, Broadstreet Health Economics & Outcomes Research; and adjunct professor, School of Pharmacy, Memorial University, Newfoundland. Johnston and colleagues sought to develop and compare benefit-risk profiles for the 3 medications using evidence from their published clinical trials.

“The safety and efficacy of these treatments have been investigated independently vs placebo but not compared in head-to-head trials. The absence of comparative data limits the ability to make evidence-based prescribing decisions,” the authors wrote in the poster. Johnston and colleagues analyzed data from the 5 randomized, placebo-controlled trials (n = 10,060) that had assessed the efficacy and safety of rimegepant 75-mg orally dissolving tablets; ubrogepant 25-mg, 50-mg, and 100-mg oral tablets; and lasmiditan 50-mg, 100-mg, and 200-mg oral tablets. The investigators found that all interventions were more effective than placebo for pain freedom and pain relief from 2 to 24 hours post dose, except for lasmiditan, which had no trial data for the 2- to 24-hour pain relief time frame.

In comparing medications, the investigators found that rimegepant 75 mg had a low number needed to treat (NNT) to achieve sustained pain freedom at 2 to 24 hours (7; 95% CI, 5-12). In comparison, ubrogepant 25 mg had an NNT of 24 (95% CI, 10-166), ubrogepant 50 mg had an NNT of 19 (95% CI, 11-49), and ubrogepant 100 mg had an NNT of 13 (95% CI, 7-33). Lasmiditan 50 mg had an NNT of 26 (95% CI, 13-95), lasmiditan 100 mg had an NNT of 20 (95% CI, 12-44), and lasmiditan 200 mg had an NNT of 12 (95% CI, 8-18). The NNT to achieve sustained pain relief at 2 to 24 hours was 5 (95% CI, 4-7) for rimegepant 75 mg, 8 (95% CI, 5-16) for ubrogepant 25 mg, 6 (95% CI, 5-9) for ubrogepant 50 mg, and 5 (95% CI, 4-8) for ubrogepant 100 mg.

Johnston and colleagues also looked at the number needed to harm (NNH) and observed that for dizziness, rimegepant 75 mg and ubrogepant 100 mg and 50 mg had a protective effect compared with placebo. Ubrogepant 25 mg had an NNH of 54 (95% CI, –1332 to 1379), lasmiditan 50 mg had an NNH of 28 (95% CI, 15-62), lasmiditan 100 mg had an NNH of 11 (95% CI, 7-17), and lasmiditan 200 mg had an NNH of 9 (95% CI, 6-15).

For nausea, the NNH was 24 (95% CI, 4-229) for rimegepant 75 mg, 99 (95% CI, –2580 to 2378) for ubrogepant 25 mg, 83 (95% CI, –3377 to 3471) for ubrogepant 50 mg, 47 (95% CI, 16-265) for ubrogepant 100 mg, 65 (95% CI, 18-485) for lasmiditan 50 mg, 72 (95% CI, 27-340) for lasmiditan 100 mg, and 49 (95% CI, 21-144) for lasmiditan 200 mg.

“In the acute treatment of migraine, all 3 active interventions were more effective than placebo, with acceptable safety profiles. Compared [with] all doses of lasmiditan and ubrogepant, the NNT to achieve immediate (2 hours) and sustained (2-24 hours) pain freedom and pain relief was lower for rimegepant 75 mg (except for lasmiditan 200 mg for pain freedom at 2 hours),” Johnston et al concluded.

REFERENCE
Intranasal DHE Agent INP104 Demonstrates Safety for Migraine Treatment

By Victoria Johnson

SAFETY DATA FROM THE RECENT long-term phase 3 STOP 301 study (NCT03557333) suggest that INP104 for the treatment of migraine has an acceptable safety profile, although safety should be monitored with intermittent use of the medication. These findings were presented in 3 posters at the 2021 American Headache Society 63rd Virtual Annual Scientific Meeting, held June 3 to 6, by Stephen Shrewsbury, MD, chief medical officer, Impel NeuroPharma,1-3

Shrewsbury and colleagues assessed the incidence of nausea, nasal safety, and cardiovascular (CV) safety of INP104. The treatment is currently being investigated for its novel delivery of dihydroergotamine mesylate (DHE), usually administered intravenously (IV), to the upper nasal space using the company’s gas-propelled Precision Olfactory Delivery device.

“Nausea associated with migraine can significantly impede migraine management by discouraging or delaying use of oral medications and/or limiting their absorption, resulting in slow onset of action. Consequently, headache severity may be prolonged and worsen, which may increase the duration of disability and disease burden,” Shrewsbury and colleagues wrote in the first poster.1

Nausea is often reported with high peak plasma DHE concentration by IV administration, so the investigators sought to determine the incidence of delivery with INP104’s nasal delivery system. They analyzed data from the full safety set of 354 patients from the STOP 301 study. Of these patients, 36.7% (n = 130) reported at least 1 treatment-related or treatment-emergent adverse event (TEAE) during the 24-week treatment period.

Over 52 weeks and 6332 doses of INP104, 30 patients reported 39 nausea TEAEs (0.6%). Most nausea TEAEs were reported during the treatment period (n = 28) and 34 were considered related to treatment. Fifteen nausea events were reported after the first dose, 9 after the second, and 4 after the third. Most nausea TEAEs were of mild (n = 22) or moderate (n = 16) severity. One patient reported a severe nausea TEAE but completed the study and was administered another 19 doses without further reports of nausea. Four patients (1.1%) discontinued treatment and 3 (0.8%) withdrew from the study because of nausea. A few patients (3.1%; n = 11) used an antiemetic or antinauseant.

“The lower rates of nausea reported in this study may be due to the lower peak plasma DHE concentration observed with INP104 compared with IV DHE. This study demonstrates the possibility for a lower incidence of the self-limiting TEAE of nausea, with the potential to offer a viable delivery alternative to DHE users,” Shrewsbury and colleagues concluded in the first poster presentation.

The same safety set of patients was evaluated for CV safety, with data presented in the second poster. The investigators found that 5 patients (1.4%) experienced vascular TEAEs over the 24-week treatment period. Of these, 4 (1.1%) experienced mild hypertension, although this either was present at baseline or resolved. One patient with hypertension withdrew because of pregnancy. Another patient experienced an unrelated hematoma from a motorcycle accident.

“DHE has long been used and recommended for the treatment of migraine due to its high response rate and sustained efficacy. However, despite over 70 years of clinical experience, DHE product labels warn of potential CV and peripheral ischemic events,” Shrewsbury and colleagues rationalized in the second presentation.2

Overall, they saw minimal mean changes from baseline for systolic and diastolic blood pressure, median heart rate, aggregate PR interval, QRS duration, QT interval, and R-R interval. Additionally, no concerning TEAEs were seen with INP104 overuse and use with contraindicated triptans.

In assessing nasal safety of INP104, the investigators found that 45.8% (n = 162) of patients reported a mild nasal TEAE in the 24-week treatment period and 58.9% (n = 43) reported the same such event during the 52-week extension. Nasal congestion was most common (16.7%; n = 59), followed by upper respiratory tract infection (10.7%; n = 38). These were mild or moderate, with the exception of 1 severe case of nasal congestion. Thirteen patients (5.0%) had mild to moderate mucosal edema, but this was not considered a concerning finding.3

TEAEs led to INP104 discontinuation in 4% (n = 14) of patients during the 24-week period and 1.4% (n = 1) in the 52-week period, mostly because of nasal congestion (1.4%; n = 5) and nasal discomfort (1.1%; n = 4).

The investigators observed minimal mean decreases and mean increases/decreases from baseline in University of Pennsylvania Smell Identification Test scores during the 24- and 52-week periods. Overall, 14 of 17 cases of olfactory reduction resolved. The Nasal Safety Review Committee concluded that the patient-reported AEs were a sufficient reason to monitor safety of intermittent use of INP104, but no safety concerns were raised from the data review.4

REFERENCES
Cutting-edge Care in Multiple Sclerosis: Advances in S1P Therapy

By Matt Hoffman

AT THE RECENT VIRTUAL "Institutional Perspectives in Neurology: Multiple Sclerosis" webinar, several presentations given by staff at Mayo Clinic addressed hot topics in the clinical care and diagnosis of multiple sclerosis (MS), including the latest in therapeutic advances and the many mimics and demyelinating disorders that present similarly to MS.

The sessions were moderated by Brian G. Weinshenker, MD, FRCPC, program chair and professor of neurology, College of Medicine, Mayo Clinic Rochester. New therapies were a main focus of the program, particularly the landscape of newly approved sphingosine 1 phosphate (S1P)–targeting oral medications for MS. That presentation was given by Jessica Stulc, MD, MPH, director, Multiple Sclerosis Treatment and Research Center, Minneapolis Clinic of Neurology, who shared insight into the currently approved therapies for relapsing-remitting MS and the mechanism of action for the new entries in the S1P class: ozanimod (Zeposia; Bristol Myers Squibb), approved in March 2020; and ponesimod (Ponvory; Janssen Pharmaceutical), approved in March 2021. Stulc began by detailing the expression and background on the receptor.

"These are G-protein–coupled receptors that work as a signaling molecule. Primarily, for MS, the function we're aware of is that it keeps the lymphocytes in the lymph nodes. You have to have signaling to allow egress of the lymphocytes out into the peripheral tissues," Stulc explained. She also clarified the 5 subtypes of S1P receptors: S1PR1, S1PR2, S1PR3, S1PR4, and S1PR5, the last of which is expressed in the white matter of the central nervous system.

Stulc then highlighted the major differences between these 2 new additions to the MS therapeutic arsenal. Ozanimod is selective in its targeting of S1PR1 and S1PR5, and it has an active metabolite. It was compared with intramuscular interferon-ß1a in both of its phase 3 clinical trials, RADIANCE (NCT01628393) and SUNBEAM (NCT02294058). On the other hand, ponesimod is selective in its targeting of only the S1PR1 receptor and has no active metabolite. In the OPTIMUM study (NCT02425644), it was compared with teriflunomide (Aubagio; Sanofi). Additionally, it is considered a rapid-acting agent.

Stulc noted that there is a titration for ozanimod, taking place over 8 days, for a 0.92-mg maintenance dose. Regarding safety outcomes with the drug, patients treated in clinical trials with the agent showed minor heart rate reductions—with an average mean decrease of 1.0 to 1.2 beats per minute in hour 5 of day 1 of dosing. The maximal effect, she noted, occurred on day 8. Additionally, an average of 1 to 2 mm Hg decrease in blood pressure was observed related to the safety outcome of hypertension.

In highlighting the prescribing information for the agent, Stulc pointed to the contraindications, specifically patients with severe and untreated obstructive sleep apnea and those concomitantly using a monoamine oxidase inhibitor.

"[The contradictions are] because of the active metabolite, [so there are] recommended prebaseline assessments. Basically, getting your updated labs, your [electrocardiogram], etc. If there's a question about other drugs that reduce heart rate, they do recommend a cardiology consult. [Optical coherence tomography] is recommended for those with a history of diabetes or uveitis," she explained.

For ponesimod, Stulc explained that the safety outcomes in the OPTIMUM trial showed a similar reduction in heart rate, with a mean decrease of 1.0 to 6.0 beats per minute on day 1 and an atrioventricular (AV) conduction delay—specifically resulting in first-degree AV block in 3.4% of patients on ponesimod versus 1.2% of patients on teriflunomide. No second- or third-degree blocks were observed. Additionally, she noted that ponesimod is contraindicated for individuals with a myocardial infarction (MI) within the past 6 months, unstable angina, stroke, transient ischemic attack, decompensated heart failure, or class III/IV heart failure. Additionally, a first-dose observation is recommended for all patients with sinus bradycardia, first- or second-degree AV block, or any history of heart failure or MI. Caution is advised, Stulc explained, when patients have severe respiratory disease.

"In terms of clinical considerations, the sequencing of the drug, the timing, the mechanism of action, and then underlying health conditions and medications your patients might be taking [should be top of mind] as you're considering these medications," Stulc concluded.
DYSFUNCTION. DESTRUCTION. NEURONAL DEATH IN ALS.

AMYOTROPHIC LATERAL SCLEROSIS (ALS) DISEASE PATHWAYS: EMERGING INSIGHTS

Advances in understanding neuronal survival and degeneration underscore the central role that the endoplasmic reticulum (ER) and mitochondria play in ALS.1-4

1. In ALS, ER stress and dysfunction, in combination with abnormal DNA transcription, lead to misfolded proteins and accumulating protein aggregates, worsening ER stress, and neuronal death.2,3,5,6

2. In ALS, mitochondrial dysfunction and release of cytochrome C, along with an imbalance of pro- and antiapoptotic factor production, trigger the mitochondrial apoptotic pathway, leading directly to neuronal death.2

Less Invasive Epilepsy Surgery May Help Turn Candidates Into Consults

Recent advances in stereoelectroencephalography and laser ablation may help convert those who may be candidates for pediatric epilepsy surgery to those who proceed with a consultation.

By Rohini K. Coorg, MD
Interim Medical Director, Epilepsy Monitoring Unit and Tuberous Sclerosis Program, Texas Children’s Hospital

The advent of stereoelectroencephalography (SEEG) coupled with MRI-guided laser interstitial thermal therapy (MRI-guided LITT) offers one such strategy useful in a number of potential scenarios, each described in detail in this article.

Prior to SEEG: Phase 1 Presurgical Epilepsy Evaluation
Before any surgical intervention may be recommended, a presurgical evaluation at an experienced epilepsy center is necessary to localize the seizure onset zone and clarify a surgical plan. Curative versus palliative goals should be discussed with families prior to and during the evaluation. This process may be divided into 2 “phases,” with only some patients requiring the second phase, invasive monitoring. As part of the phase 1 study, noninvasive diagnostic techniques such as a careful history and physical examination, structural neuroimaging (3 Tesla MRI), continuous video electroencephalogram, and neuropsychological testing are most important in confirming the presence of focal, multifocal, or generalized epilepsy and localization of seizure onset. On an individualized basis, additional functional neuroimaging studies may further assist with definition of the seizure onset zones in relation to eloquent brain regions, particularly in a nonlesional case. These include fluorodeoxyglucose F 18 positron emission tomography and task-based and resting-state functional brain MRI. Additional neurophysiology studies include subtraction of interictal from ictal single-photon emission computed tomography, magnetoencephalography, and brain electrical source analysis.
Transcranial magnetic stimulation may assist in identification of eloquent motor areas. If permanent postoperative language or memory deficits remain a concern despite the noninvasive techniques mentioned, the Wada (intracarotid sodium amobarbital) procedure may be utilized to assist in lateralization of these important functions.

Results of all studies are carefully discussed and assessed for any localizing features or deficits during a multidisciplinary epilepsy surgery conference with epileptologists, neurosurgeons, neuroradiologists, and neuropsychologists. Based on group consensus, a surgical plan may be offered. In cases determined to have a reasonable chance for meaningful reduction or cure for seizures and with data that appear incomplete or suggestive of multiple onsets, a plan for invasive monitoring (a phase 2 study) may be recommended.

**SEEG: Phase 2 Presurgical Evaluation**

Subdural and depth electrodes were utilized as early as 1959 to study the onset and evolution of seizures. The Montreal Neurological Institute established SEEG as a useful localizing tool in 1972. SEEG allows for direct recording of deeper, often bilateral, and disparate cortical areas through a minimally invasive approach. SEEG electrodes may be placed in the operating room under general anesthesia via a small twist-drill hole utilizing a conventional stereotactic frame, frameless stereotactic system, or robotic assistance. Precise placement of electrodes is mandatory to adequately sample epileptogenic regions and circumvent important vascular structures. Robotic assistance is a relatively recent advance in technology that has been established as safe, accurate, and efficient in the pediatric population. Studies have estimated hemorrhage risk utilizing SEEG to be similar to the 4% reported in subdural grid cases, but the infection risk of 1% with SEEG is lower than a reported 3% infection risk for grid cases. Additional studies recommend caution when using more than 13 electrodes, especially in older patients with prior surgeries, noting a 0.2% risk for symptomatic hemorrhage per electrode.

For each patient, electrode placement relies on a well-developed hypothesis, with electrodes sampling the proposed onset(s) and evolution of seizures based on clinical semiology and noninvasive diagnostic studies obtained during phase 1. Trajectories are planned with consideration for potential laser ablation utilizing phase 1 data for targeted coverage—an approach termed dynamic SEEG. Typical scenarios for utilizing SEEG include bitemporal epilepsy, discerning between frontal or temporal epilepsy, and nonlesional epilepsy, or when an area outside an obvious lesional region may be implicated (ie, “mesial temporal plus” cases).

As SEEG has become more widely used, as well as robotic assistance, TCH has placed SEEG electrodes in children as young as 12 months. Skull thickness remains an important factor in maintaining the security of bolt and electrode placement. We have utilized as many as 39 individual depth electrodes in a single patient in our practice to date.

If amplifier space allows, scalp electrodes may be placed (typically while the patient is still in the operating room) to assist in discerning epileptic from nonepileptic events, particularly if the area covered by SEEG electrodes is limited. If the SEEG coverage outnumbers amplifier capacity, recording from every other contact may be performed in electrodes furthest away from the suspected onset and adjusted as needed over the admission.

In our practice at TCH, when the patient’s typical epileptic seizures are recorded without SEEG change, additional SEEG electrodes may be placed based on the recorded propagation pattern of the seizure to confirm ictal onset and clarify the surgical plan during the same admission. This has been demonstrated as safe at other centers as well. Functional mapping may be performed via SEEG electrodes to identify eloquent motor or language regions on an individualized basis, though this may be limited by electrode coverage. Lower maximum stimulation parameters should be used compared with subdural grids due to an increased electrode surface area in contact with brain tissue. Cortical stimulation of SEEG electrodes may also be done to elicit typical seizures to test a hypothesis regarding ictal onset.

**MRI-Guided LITT**

Following data collection with SEEG and identification of a surgical target, a surgical plan is generated and electrodes are explanted. Depending on the specific patient scenario, MRI-guided LITT may be utilized immediately following electrode removal under the same sedation encounter or, if needed, at a later date. Two systems have been approved by the FDA in the treatment of solid tumors and focal epilepsies: Medtronic’s Visualase in 2007 and Monteris Medical’s NeuroBlate in 2009.

The Visualase system allows for the immediate replacement of SEEG electrode in the operating room with a 1.6-mm fiber-optic, laser-tipped catheter using the same bolts and trajectories, with a 14- to 16-mm ablation volume diameter. The Monteris system requires a separate procedure for catheter insertion because of its 3.3-mm probe size but has the ability for a larger (3.5-cm) diameter of ablation.

A brain MRI is performed to confirm laser probe placement. During the ablation procedure, infrared laser energy is directed at the surgical target, resulting in increased temperature and localized coagulative necrosis monitored on MRI thermography. The laser fibers may be moved along the trajectories to target additional regions for ablation. Important limitations include proximity to areas with a cooling effect on surrounding brain tissue, such as blood vessels, ventricles, and prior resection sites. These structures have the potential to affect the extent of an ablation plan. Pulsation artifact and fixation devices may impair interpretation of the thermogram. Following ablation and confirming destruction of the intended target, imaging is performed again to evaluate for the presence of unexpected hemorrhage. Postoperatively, most patients are discharged within a day or two after the procedure.

MRI-guided LITT has been utilized in multiple pediatric epilepsy scenarios, including tuberous sclerosis complex (TSC), focal cortical dysplasia, temporal lobe epilepsy, hypothalamic hamartoma, periventricular heterotopia, and insular epilepsies. Further, MRI-guided LITT may be considered as a minimally invasive alternative to corpus callosotomy with similar long-term results. Most of these published series involve relatively small numbers of pediatric patients, with success depending on the ability to both identify and ablate the entire epileptogenic region. Multiple laser trajectories may be utilized in this scenario.
Severe complications were reported for 3.4% of patients and include (depending on the specific location of ablation) postoperative weakness, diabetes insipidus, trapped right ventricle with obstructive hydrocephalus and bilateral papilledema, and short-term memory deficits. Of the remaining patients, 78% experienced no complications and 19% experienced transient mild complications including hemiparesis, weakness, edema, delayed wound healing, hypotension, transient increase in gelastic seizures (with ablation targeting a hypothalamic hamartoma), stuttering, expressive language dysfunction, short-term memory dysfunction, ipsilateral Horner syndrome, and subclinical asymptomatic subarachnoid hemorrhage.

Larger systematic disease-specific studies are needed to provide more informed comparisons of risks, benefits, and long-term outcomes between the minimally invasive approach of MRI-guided LITT and their “maximally invasive” counterparts.

Case Example No. 1

**PATIENT EU IS A FORMER-TERM**, right-handed 4-year-old girl with a diagnosis of TSC associated with TSC2 at seizure onset at age 6 weeks. Her seizures occurred up to 30 times daily, remained refractory since onset, and evolved into infantile spasms at age 10 months. She was referred to our institution by Cincinnati Children’s Hospital Medical Center at age 32 months for a presurgical epilepsy evaluation, with neuroimaging revealing bilateral cortical tubers (Figure 1). She underwent SEEG/phase 2 placement at age 38 months with electrode placement based on noninvasive/phase 1 data. After nonlocalizing ictal signatures were recorded, additional SEEG electrodes were placed for a total of 25 electrodes (Figure 2). With this additional coverage, focal seizures were localized on SEEG to a tuber in the right prefrontal gyrus (Figure 3). Functional mapping was performed, which confirmed that the ictal onset zone did not overlap with eloquent motor regions (Figure 4). She underwent MRI-guided LITT of this tuber with 2 trajectories (Figure 5) and remains clinically seizure free at 21 months postop (Engel Epilepsy Surgical Outcome Scale class I).

**FIGURE 1. T2-FLAIR MRI Brain Coronal Images Showing Bilateral Cortical Tubs Consistent With TSC**

T2-FLAIR, T2-weighted fluid-attenuated inversion recovery; TSC, tuberous sclerosis complex.

**FIGURE 2. Case No. 1 SEEG Electrode Coverage**

<table>
<thead>
<tr>
<th>Electrode</th>
<th>Name</th>
<th>Reference</th>
<th>Left/Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LIF</td>
<td>Left Infantilobar</td>
<td>E</td>
</tr>
<tr>
<td>2</td>
<td>WIP</td>
<td>Right Infantilobar</td>
<td>P</td>
</tr>
<tr>
<td>3</td>
<td>RMIF</td>
<td>Right Middle Frontal Gyrus</td>
<td>P</td>
</tr>
<tr>
<td>4</td>
<td>RMIFCA</td>
<td>Right Middle Frontal Gyrus-CA</td>
<td>P</td>
</tr>
<tr>
<td>5</td>
<td>RMIFCA</td>
<td>Right Middle Frontal Gyrus-CA</td>
<td>P</td>
</tr>
<tr>
<td>6</td>
<td>WMIF</td>
<td>Right Middle frontal lobe</td>
<td>P</td>
</tr>
<tr>
<td>7</td>
<td>ROSSA</td>
<td>Right Spinal accessory motor area</td>
<td>S</td>
</tr>
<tr>
<td>8</td>
<td>MIF</td>
<td>Right Motor Face</td>
<td>F, S</td>
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<td>WIMF</td>
<td>Right Motor Face</td>
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<td>RMK</td>
<td>Right Motor Hand</td>
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<td>13</td>
<td>NMI</td>
<td>Right Maxillary Nasal Area</td>
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<td>S</td>
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<td>WIF</td>
<td>Right Inferior Frontal lobule</td>
<td>A</td>
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<td>17</td>
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<td>A</td>
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<td>18</td>
<td>LMTG</td>
<td>Left Middle Temporal gyrus</td>
<td>A</td>
</tr>
<tr>
<td>19</td>
<td>LPS</td>
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<td>S</td>
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<tr>
<td>20</td>
<td>LSP</td>
<td>Left Superior Parietal lobule</td>
<td>S</td>
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<tr>
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<td>RMIFCA*</td>
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<tr>
<td>23</td>
<td>ROSSA*</td>
<td>Right Motor hand anterior</td>
<td>F</td>
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<td>24</td>
<td>RIF</td>
<td>Right sensory face</td>
<td>A, F</td>
</tr>
<tr>
<td>25</td>
<td>ROSSA*</td>
<td>Right Supraorbital motor area anterior</td>
<td>A, B</td>
</tr>
</tbody>
</table>

EEG, electroencephalogram; FDG-PET, fluorodeoxyglucose; F 18 positron emission tomography; MEG, magnetoencephalography; RIMFG, right intermediate middle frontal gyrus; SEEG, stereoelectroencephalography.

List of 25 electrodes sampling multiple regions within the right and left hemispheres using the following rationale: A: anatomy; E: scalp ictal/interictal EEG; P: FDG-PET; F: functional/eloquent area; S: semiology; Mc: MEG cluster. Additional electrodes implanted during the admission are denoted by an asterisk. Image reprinted with permission from Cemal Karakas, MD.

**FIGURE 3. SEEG Ictal Onset of a Typical Clinical Seizure Appearing as Low-Amplitude Fast Activity in RIMFG 1-4, Evolving Into Sharp and Slow Wave Discharges**

RIMFG, right intermediate middle frontal gyrus; SEEG, stereoelectroencephalography.

**FIGURE 4. Functional Motor Mapping With SEEG Electrodes Identifying Left Foot, Left Arm, Mouth, and Left Hand Regions**

Functional Mapping with SEEG electrodes

SEEG, stereoelectroencephalography. Image reprinted with permission from Cemal Karakas, MD.
NEW INDICATION

Dissolving the line between acute and preventive treatment for migraines\textsuperscript{1,2}

Finally, the first and only medication proven\textsuperscript{1,2}:

\textbf{FAST}

• One rapidly dissolving tablet that works quickly to \textit{resolve pain} and return many patients back to normal activities in 1 hour\textsuperscript{1,3,5}

• Demonstrated \textit{preventive effect within 1 week} for many patients \textsuperscript{4,6}

\textbf{LASTS}

• Treats or prevents for \textit{up to 48 hours} at a time for many patients \textsuperscript{1,3,7}

• Reduction in mean monthly migraine days (MMDs) for many patients \textit{through 12 weeks of treatment}\textsuperscript{1,2}

See study results below.

\textbf{So you can TREAT \textcircled{R} PREVENT}

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\*Exploratory analysis. Subjects had \ge 1 day of efficacy data in the observation period and in the first week of the double-blind treatment period.\textsuperscript{6}

Up to 18 doses of Nurtec ODT can be taken per month.\textsuperscript{1}

For the acute indication, Nurtec ODT was evaluated in a multi-center, double-blind, randomized, placebo-controlled study of 1351 patients (Nurtec ODT 75 mg, n=669; placebo, n=682), with co-primary endpoints at 2 h for Nurtec ODT vs placebo: pain freedom (21% vs 11%, \( P < .001 \)) and freedom from most bothersome symptom (MBS; predefined as photophobia, phonophobia, or nausea; 35% vs 27%, \( P = .001 \)).\textsuperscript{1}

For the preventive indication, Nurtec 75 mg was evaluated in a multi-center, double-blind, randomized, placebo-controlled study of 695 patients (Nurtec 75 mg, n=348; placebo, n=347) with the primary endpoint being change from baseline in the mean number of monthly migraine days during weeks 9-12 (-4.3 vs -3.5, \( P = .01 \)).\textsuperscript{1}

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\textbf{INDICATION}

Nurtec ODT is indicated in adults for the:

• acute treatment of migraine with or without aura

• preventive treatment of episodic migraine

\textbf{SELECT IMPORTANT SAFETY INFORMATION}

\textbf{Contraindications:} Hypersensitivity to Nurtec ODT or any of its components.

Please see additional Important Safety Information and the accompanying Brief Summary of Full Prescribing Information on the following pages.
Real patients like Ellie are managing their migraines with Nurtec ODT

Ellie is an actual patient who takes Nurtec ODT for either acute or preventive treatment of her migraines.

“Nurtec ODT meets my personal needs. I know that stress is a trigger during the school year—especially before college exams. I want to control my migraine on MY TERMS.”

- Ellie W

INDICATION
Nurtec ODT is indicated in adults for the:
• acute treatment of migraine with or without aura
• preventive treatment of episodic migraine

IMPORTANT SAFETY INFORMATION
Contraindications: Hypersensitivity to Nurtec ODT or any of its components.

Warnings and Precautions: If a serious hypersensitivity reaction occurs, discontinue Nurtec ODT and initiate appropriate therapy. Serious hypersensitivity reactions have included dyspnea and rash, and can occur days after administration.

Adverse Reactions: The most common adverse reactions were nausea (2.7% in patients who received Nurtec ODT compared to 0.8% in patients who received placebo) and abdominal pain/dyspepsia (2.4% in patients who received Nurtec ODT compared to 0.8% in patients who received placebo). Hypersensitivity, including dyspnea and rash, occurred in less than 1% of patients treated with Nurtec ODT.

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Please see Brief Summary of Full Prescribing Information on the next page.


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BRIEF SUMMARY OF PRESCRIBING INFORMATION
(For complete product information, see Full Prescribing Information.)
NURTEC® ODT (rimegepant) orally disintegrating tablets 75 mg, for sublingual or oral use

1 INDICATIONS AND USAGE
1.1 Acute Treatment of Migraine
NURTEC ODT is indicated for the acute treatment of migraine with or without aura in adults.

1.2 Preventive Treatment of Migraine
NURTEC ODT is indicated for the preventive treatment of episodic migraine in adults.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing for Acute Treatment of Migraine
The recommended dose of NURTEC ODT is 75 mg taken orally, as needed. The maximum dose in a 24-hour period is 75 mg. The safety of using more than 18 doses in a 30-day period has not been established.

2.2 Recommended Dosing for Preventive Treatment of Episodic Migraine
The recommended dosage of NURTEC ODT is 75 mg taken orally every other day.

4 CONTRAINDICATIONS
NURTEC ODT is contraindicated in patients with a history of hypersensitivity reaction to rimegepant, NURTEC ODT, or any of its components. Delayed serious hypersensitivity has occurred [see Warnings and Precautions (5.1)].

5 WARNING AND PRECAUTIONS
5.1 Hypersensitivity Reactions
Hypersensitivity reactions, including dyspnea and rash, have occurred with NURTEC ODT in clinical studies. Hypersensitivity reactions can occur days after administration, and delayed serious hypersensitivity has occurred. If a hypersensitivity reaction occurs, discontinue NURTEC ODT and initiate appropriate therapy [see Contraindications (4)].

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:
• Hypersensitivity Reactions [see Warnings and Precautions (5.1)]

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.

Acute Treatment of Migraine
The safety of NURTEC ODT for the acute treatment of migraine in adults has been evaluated in a randomized, double-blind, placebo-controlled trial (Study 1) in 682 patients with migraine who received one 75 mg dose of NURTEC ODT [see Clinical Studies (14)]. Approximately 85% were female, 74% were White, 21% were Black, and 17% were Hispanic or Latino. The mean age at study entry was 40 years (range 18-75 years of age).

Long-term safety was assessed in an open-label extension study using a different oral dosage form of rimegepant. That study evaluated 1,798 patients, dosing intermittently for up to 1-year, including 1,131 patients who were exposed to rimegepant 75 mg for at least 6 months, and 863 who were exposed for at least one year, all of whom treated an average of at least two migraine attacks per month.

The most common adverse reaction in Study 1 was nausea (2% in patients who received NURTEC ODT compared to 0.4% of patients who received placebo). Hypersensitivity, including dyspnea and severe rash, occurred in less than 1% of patients treated with NURTEC ODT [see Contraindications (4) and Warnings and Precautions (5.1)].

Preventive Treatment of Episodic Migraine
The safety of NURTEC ODT for the preventive treatment of episodic migraine in adults has been established in a randomized, double-blind, placebo-controlled trial with an open-label extension (Study 2) using a different oral dosage form of rimegepant [see Clinical Studies (14)]. In the 12-week, double-blind treatment period, 370 patients with migraine received one 75 mg dose of rimegepant every other day. Approximately 81% were female, 80% were White, 17% were Black, and 28% were Hispanic or Latino. The mean age at study entry was 41 years (range 18-74 years of age). Long-term safety was assessed in an open-label extension study that included 603 patients who were treated for up to one year. Overall, 527 patients were exposed to rimegepant 75 mg for at least 6 months, and 311 were exposed for at least one year.

The most common adverse reactions (occurring in at least 2% of rimegepant-treated patients and at a frequency of at least 1% higher than placebo) in Study 2 were nausea (7.7% in patients who received rimegepant compared with 0.6% of patients who received placebo) and abdominal pain/dyspepsia (2.4% in patients who received rimegepant compared with 0.8% of patients who received placebo).

7 DRUG INTERACTIONS
7.1 CYP3A4 Inhibitors
Concomitant administration of NURTEC ODT with strong inhibitors of CYP3A4 results in a significant increase in rimegepant exposure. Avoid concomitant administration of NURTEC ODT with strong inhibitors of CYP3A4 [see Clinical Pharmacology (12.3)].

Concomitant administration of NURTEC ODT with moderate inhibitors of CYP3A4 may result in increased exposure of rimegepant. Avoid another dose of NURTEC ODT within 48 hours when it is concomitantly administered with moderate inhibitors of CYP3A4 [see Clinical Pharmacology (12.3)].

7.2 CYP3A Inducers
Concomitant administration of NURTEC ODT with strong or moderate inducers of CYP3A4 can result in a significant reduction in rimegepant exposure, which may lead to loss of efficacy of NURTEC ODT. Avoid concomitant administration of NURTEC ODT with strong or moderate inducers of CYP3A4 [see Clinical Pharmacology (12.3)].

7.3 Transporters
Rimegepant is a substrate of P-gp and BCRP efflux transporters. Concomitant administration of NURTEC ODT with inhibitors of P-gp or BCRP may result in a significant increase in rimegepant exposure [see Clinical Pharmacology (12.3)]. Avoid NURTEC ODT with inhibitors of P-gp or BCRP.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate data on the developmental risk associated with the use of NURTEC ODT in pregnant women. In animal studies, oral administration of rimegepant during organogenesis resulted in adverse effects on development in rats (reduced fetal body weight and increased incidence of fetal variations) at exposures greater than those used clinically and which were associated with maternal toxicity. The evaluation of developmental effects following oral administration of rimegepant throughout pregnancy and lactation was inadequate (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 estimated rate of major birth defects (2.2 to 2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk
Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

8.2 Lactation
There are no data on the presence of rimegepant or its metabolites in human milk, the effects of rimegepant on the breastfed infant, or the effects of rimegepant on milk production. There are no animal data on the excretion of rimegepant in milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for NURTEC ODT and any potential adverse effects on the breastfed infant from NURTEC ODT or from the underlying maternal condition.

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

8.5 Geriatric Use
In pharmacokinetic studies, no clinically significant pharmacokinetic differences were observed between elderly and younger subjects. Clinical studies of NURTEC ODT did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment
No dosage adjustment of NURTEC ODT is required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Plasma concentrations of rimegepant were significantly higher in subjects with severe (Child-Pugh C) hepatic impairment. Avoid use of NURTEC ODT in patients with severe hepatic impairment [see Clinical Pharmacology (12.3)].

8.7 Renal Impairment
No dosage adjustment of NURTEC ODT is required in patients with mild, moderate, or severe renal impairment. NURTEC ODT has not been studied in patients with end-stage renal disease and in patients on dialysis. Avoid use of NURTEC ODT in patients with end-stage renal disease (Clcr < 15 mL/min) [see Clinical Pharmacology (12.3)].

10 OVERDOSAGE
There is limited clinical experience with NURTEC ODT overdosage. Treatment of an overdose of NURTEC ODT should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. No specific antidote for the treatment of rimegepant overdose is available. Rimegepant is unlikely to be significantly removed by dialysis because of high serum protein binding [see Clinical Pharmacology (12.3)].

Manufactured for:
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**FIGURE 5.** MRI Brain, DWI Images Showing Edema Immediately Following MRI-guided LITT Procedure

The RIMFG and RMFGc electrodes were removed and replaced by a laser catheter using the same bolts and trajectories to target the epileptogenic cortical tuber in the right prefrontal region.

DWI, diffusion-weighted imaging; MRI-guided LITT, MRI-guided laser interstitial thermal therapy; RIMFG, right intermediate middle frontal gyrus.

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**Case Example No. 2**

**PATIENT SR IS A FORMER-TERM,** right-handed 18-year-old man with seizure onset at age 22 months attributed to an extensive dysembryoplastic neuroepithelial tumor (**FIGURE 6**). Following presentation, he underwent craniotomy with resection and biopsy. He later required a partial resection with right temporal lobectomy and underwent proton beam radiation at approximately age 3 and 5 years, respectively. Just prior to age 6 years, he developed a large tumor cyst that required stereotactic drainage and placement of an indwelling Ommaya reservoir.

Since onset, his focal seizures appeared as an arousal from sleep, moan, or loud cry with tachycardia, hyperventilation, and oral automatisms, evolving into left hemitonic movements and left-hand dystonia. A vagus nerve stimulator was placed at age 8 years. He underwent MRI-guided LITT of residual tumor at age 11 years, which did not change or improve his seizure burden. A year later, following a repeat surgical evaluation, SEEG/phase 2 utilizing 6-depth electrodes was performed but failed to localize ictal onset, and surgery was not pursued.

Given significant advances in technology and our increased institutional experience, our patient underwent a repeat SEEG/phase 2 study at age 17 years, ultimately utilizing 39 electrodes targeting both lesional and nonlesional regions. Coverage focused on the right temporal and insular regions with electrodes targeting the hypothesized onset and network (**FIGURE 7**). Seizures had broad, nonstereotyped ictal onset in electrodes within the right insular regions with rapid temporal spread (**FIGURE 8**). Because of concerns of multifocal onset within this region, the conference consensus was to offer an insular ablation followed by repeat craniotomy and generous right temporal resection. MRI-guided LITT was performed utilizing trajectories of 4 electrodes sampling the insular regions (**FIGURE 9**). The plan for subsequent right temporal lobectomy was canceled when the patient remained seizure free at 4.5 months following insular ablation. This is his longest period of seizure freedom since onset (Engel Epilepsy Surgical Outcome Scale class 1).

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**FIGURE 6.** Extensive Right Hemispheric Dysembryoplastic Neuroepithelial Tumor Found at 22 Months After Presenting Seizure

Top: Axial T2-FLAIR MRI brain images show a large right hemispheric DNET at age 22 months. Bottom: Coronal T2 MRI brain sequences from the same study provide an additional view of the large right hemispheric DNET, which involves the right insular structures and extends deep into the basal ganglia.

DNET, dysembryoplastic neuroepithelial tumor; T2-FLAIR, T2-weighted fluid-attenuated inversion recovery.

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**FIGURE 7.** Case No. 2 SEEG Electrode Coverage

**Right:** List of 39 electrodes sampling multiple right hemispheric regions and the left posterior insular long gyrus based on the following rationale: s: semiology; m: MEG; a: anatomy; P: FDG-PET; Mc: MEG cluster; i: scalp ictal/interictal EEG.

Left, top: Reconstruction of 5 right insular electrodes superimposed on sagittal MRI brain images. Dark green: RAIASG; purple: RAIMSG; orange: RAPIALG; bright green: RPLIPG.

Left, bottom: Three-dimensional model of SEEG electrode placement.

EEG, electroencephalography; FDG-PET, fluorodeoxyglucose F 18 positron emission tomography; MEG, magnetoencephalography; SEEG, stereoelectroencephalography.

Images reprinted with permission from Kimberly Houck, MD.
Outcomes and Future Directions
Few pediatric series have published early outcomes of surgeries combining the use of SEEG with MRI-guided LITT, with one describing 2 children with TSC and 2 adolescent/young adults with focal cortical dysplasia experiencing Engel I or II outcomes between 5 and 16 months following ablation. The authors conclude that the ideal patients to benefit from this approach are those with small, bilateral, and disparate epileptogenic foci visualized on neuroimaging, such as TSC and periventricular nodular heterotopia.

In palliative epilepsy surgeries, the minimally invasive approach of combining SEEG with MRI-guided LITT is favorable and may seem more palatable to families, especially when reoperation may be a consideration in the future. In some of these cases, the risk of an open craniotomy, subdural grid placement, and/or large resection may not be balanced by expected long-term seizure freedom or normalization of development.

The cases included in this review illustrate the utility of a minimally invasive approach in a child with bilateral lesions and discordant phase 1 data and in an adolescent with a history of multiple brain surgeries and seizures originating from deep structures within the brain. In both cases, reimplantation of SEEG electrodes during the admission helped clarify ictal onset when the initial SEEG coverage failed to do so. Following MRI-guided LITT, both cases resulted in seizure freedom.

Seizure freedom and improvement of sedative adverse effects from medications are the ideal goals, but there may be additional benefits to surgery. Maximizing quality of life and development may be more realistic goals than seizure freedom for children with highly refractory epilepsy such as TSC. Improvements in development may occur without complete seizure freedom and may also be underestimated with existing measures. And finally, in adults, a relative seizure reduction is similar to complete seizure freedom when predicting quality of life following surgery. These points, along with a shifting risk-benefit ratio offered by minimally invasive diagnostic and surgical techniques, suggest that more children may benefit from surgery than previously believed.

At first glance, combining an SEEG procedure with the expectation of an ablation to immediately follow appears very attractive. However, it is important to remember that in the pediatric population, outcomes with MRI-guided LITT have been studied less extensively than more traditional methods. This paucity in research may be due to the increased complexity and heterogeneity of our patients; however, understanding when “maximally” should be preferred over “minimally” invasive approaches is still needed to prevent unnecessary or incomplete procedures. And finally, recognizing the full impact of intervening during a developmentally critical period coupled with accurate identification of the most relevant outcome measures will clarify when surgery of any type should be preferred over additional medication trials. With this, it is our hope that tangible and lasting clinical improvements may be experienced by our patients and their families over their lifetimes.
GHB as a GABA Receptor Agonist for Narcolepsy Therapy

By Jennifer S. Sun, PhD

NARCOLEPSY IS A CHRONIC SLEEP DISORDER that can have debilitating consequences. The disorder typically begins in childhood or adolescence, with mild initial symptoms that can worsen with time. Narcolepsy is increasingly recognized as an autoimmune disorder, whereby the immune system reacts to an external trigger (eg, viral) in such a way that it attacks the brain cells (ie, hypocretin neurons) that synthesize a neuropeptide (ie, hypocretin) that regulates wakefulness and sleep. However, the exact cause remains unknown; genetic risk factors or environmental triggers may precede the loss of hypocretin neurons and subsequent hormone imbalances characteristic of the disorder. Because of heterogeneity in the development and severity of symptoms, many individuals do not receive narcolepsy diagnosis until years after onset.

Narcolepsy features excessive daytime sleepiness (EDS), sudden loss of muscle tone (cataplexy), disturbed nocturnal sleep, and hypnagogic and/or hypnopompic hallucinations. EDS affects all patients with narcolepsy and is often a primary symptom, accompanied by bouts of irresistible “sleep attacks” that occur without warning and can last up to several minutes. Narcolepsy is categorized into 2 major types based on the presence/absence of cataplexy and the level of hypocretin: type 1, cataplexy present and hypocretin low; and type 2, cataplexy absent and hypocretin normal. Cataplexy is a particularly disruptive symptom that is unique to narcolepsy that can leave patients fully immobile while they maintain conscious awareness. Consequently, those with type 1 narcolepsy can experience more severe symptoms.

Sleep and wakefulness are regulated by interconnected brain circuits that modulate systems of neurotransmitters such as norepinephrine, serotonin, dopamine, histamine, and hypocretin (FIGURE). The most important inhibitory neurotransmitter of the mammalian central nervous system (CNS) is γ-aminobutyric acid (GABA), which can promote feelings of happiness and sedation. GABA-containing neurons that originate in the ventrolateral and median preoptic areas of the hypothalamus inhibit wake-promoting neurons, which promotes non–rapid eye movement (REM) sleep. GABAergic neurons in the ventral medulla mediate the inhibition of motor neurons, whereas those in the amygdala can trigger cataplexy upon evoking positive emotions. Targeting GABA receptors may therefore enable regulation of sleep duration, mediate muscle tone, and prevent overstimulation.

γ-Hydroxybutyrate (GHB or oxabrate), a physiological compound present in the human body as both a precursor and degradation product of GABA, acts as an agonist of dedicated GHB receptors (GABAA type) and GABAB receptors. GHB is present at the highest concentrations within the striatum of the developing brain, although it is also present at lower levels in other brain regions and tissues such as heart, liver, kidney, muscle, and brown fat. When sufficiently high levels of GHB are achieved through exogenous delivery, the neurotransmitter acts as a GABAB receptor agonist to increase sleep efficiency; specifically, GHB binds GABAB receptors to inhibit dopamine release by modulating central cholinergic and serotonergic neurons. GHB has also been demonstrated to dampen the baseline activity of noradrenaline-releasing neurons to a low level that still permits maintenance of muscle tone. GHB at high concentrations is thus regarded as a depressant.

Because narcolepsy has no known cure, current therapies focus on symptom management; for example, GHB has been proven effective in reducing EDS and both the frequency and severity of cataplexy episodes. Synthetic GHB is a highly hygroscopic compound that is amenable to oral administration. This exogenous GHB is absorbed and metabolized rapidly, reaching a peak plasma concentration 30 to 90 minutes after ingestion and decaying with a half-life of approximately 60 minutes. GHB has been shown to reduce the activity of patients’ thalamic, hippocampal, and neocortical neurons. Serotonin turnover in the brain is consequently increased, promoting slow-wave sleep. Dopamine release is also inhibited, improving sleep efficiency. GHB treatment is thus able to counteract sleep latency, promoting the deep, slow-wave, non-REM sleep that is severely lacking in individuals with narcolepsy.

Sodium oxybate (Xyrem; Jazz Pharmaceuticals), is the standard of care for the treatment of EDS and cataplexy in patients with narcolepsy and is FDA approved for those aged 7 years and older. Enrolled patients were either sodium oxybate naive (70%) or already on a sodium oxybate regimen (30%). Most patients were White (69%) and male (59%), with a median age of 12 years, and had received a diagnosis of narcolepsy with cataplexy a median of 1 to 2 years prior. Treatment-naive patients first received dose titration to an effective and tolerable sodium oxybate dose (ranging from 3-9 g) over 3 to 10 weeks. Following a stable-dose period of 2 to

FIGURE. Wakefulness Regulation and FT218 Compared With Xyrem

(A) Wakefulness regulation by hypocretin neurons. (B) FT218 (once-nightly SO) compared with Xyrem (twice-daily SO).
3 weeks, participants were then randomly assigned to either continue sodium oxybate treatment or switch to placebo for a 2-week double-blind treatment (randomized withdrawal) period. During the subsequent 47-week open-label safety period, all patients received sodium oxybate. The primary end point was change in the weekly number of cataplexy episodes from the end of the stable-dose period to the end of the treatment period. Secondary end points included changes in the severity of cataplexy episodes (measured with the Clinical Global Impression-Improvement [CGI-I] scale) and in EDS (measured with the Epworth Sleepiness Scale [ESS]) over the same period. Patients on a median 7-g dose of sodium oxybate showed significant improvements in the number of weekly cataplexy episodes by week 2 (median of 21 weekly cataplexy attacks in weeks 1 and 2 of the double-blind treatment period for placebo vs 6 for treatment), in the severity of attacks (66% worse for placebo vs 17% worse for treatment), and in EDS (median change in ESS score of +3 for placebo vs 0 for treatment). Adverse events (AEs), which were reported by 72% of patients, were mostly mild or moderate and were resolved without changing the sodium oxybate dose. Taken together, results to date provide strong evidence of the effectiveness of sodium oxybate in managing EDS and cataplexy.

Xywav (JZP-258; Jazz Pharmaceuticals) is an oxybate formulation that contains the same active moiety as Xyrem but a different blend of cations (calcium, magnesium, potassium, and sodium) to reduce sodium intake by 92%. Similar to Xyrem, Xywav is prescribed for the treatment of narcolepsy-associated EDS or cataplexy in patients as young as 7 years. FDA approval was granted in 2020 after successful demonstration of efficacy and safety in a multicenter phase 3, placebo-controlled, double-blind, randomized withdrawal study (NCT03030599). Patient selection criteria included a history of at least 14 cataplexy attacks within a typical 2-week period in the absence of narcolepsy treatment. Exclusion criteria included participants whose narcolepsy was secondary to another medical condition and individuals with major depression or a history of psychotic disorders, among others. The study enrolled 201 patients aged 18 to 70 years, the majority of whom were White (88.1%) and female (60.7%). Patients were categorized based on use of cataplexy treatments at study entry: sodium oxybate (Xyrem) only, sodium oxybate plus another anticataplectic, an anticatapleptic other than sodium oxybate, or no anticataplectic medication. Use of stimulants at study entry was allowed, with 39% of patients on stimulants at study entry maintaining a stable dose of stimulants throughout the trial. Patients not on sodium oxybate therapy at entry immediately began Xywav at 4.5 g per night, whereas those already taking sodium oxybate were switched to Xywav at the same dosage as the sodium oxybate. After 2 weeks, the dose was titrated up at nightly steps of 1.5 g to a stable, tolerable, and effective level over the following 8 weeks (maximum 9 g per night). Anticataplectics other than sodium oxybate were tapered down after 2 weeks and discontinued by week 10. After dose titration, all patients remained on the optimal dose of Xywav for a 2-week stable-dose period before being randomized to either continue Xywav treatment or switch to placebo for a 2-week double-blind randomized withdrawal period. The primary end point was change in the weekly number of cataplexy attacks from during the stable-dose period to during the randomized withdrawal period. The key secondary end point was change in EDS (measured with ESS) during the same interval. Overall, Xywav was determined to have superior efficacy to placebo; patients randomized to the latter experienced significantly more weekly cataplexy attacks and worse EDS than those who remained on Xywav. Although 76.1% of participants randomized to Xywav reported AEs, the symptoms were generally mild or moderate in severity. A phase 4 clinical trial (NCT0479449113) and a noninterventional trial (NCT04803786) are currently under way to examine the real-world effects of transitioning from sodium oxybate to Xywav.

FT218 (Avadel Pharmaceuticals) is a new sodium oxybate drug that was granted orphan drug designation by the FDA in 2021 for use in adults with type 1 and 2 narcolepsy. The advantage of FT218 lies in its once-nightly formulation compared with twice-nightly Xyrem or Xywav doses, which is possible due to Avadel’s trademarked microparticle-based technology (MicroPump26) that delivers a blend of immediate- and controlled-release pellets. Four phase 1 crossover, single-dose studies (pilot, dose-proportionality, relative bioavailability, and food-effect studies) have demonstrated the effectiveness of a single 4.5- to 9-g dose of FT218 in improving nocturnal sleep consolidation. Results showed that peak plasma concentration was reached at a median of 2 hours post administration compared with the short tmax of 30 minutes for the first dose of twice-nightly sodium oxybate (Figure B). The half-life of FT218 was also longer compared with Xyrem (4 hours vs 1.5 hours). Although the maximum concentration of GHB was lower with FT218 than with the 2-dose Xyrem, exposure duration was maintained. Results further showed a predictable pharmacokinetic profile for FT218 that was less affected by coincident food intake compared with Xyrem. The phase 3, placebo-controlled, double-blind, randomized, multicenter REST-ON trial (NCT02720744) assessed the efficacy and safety of FT218 for treating EDS and cataplexy in adult patients with narcolepsy. FT218 benefited patients with both type 1 and 2 narcolepsy, with CGI-I data revealing significantly more patients with improved EDS compared with placebo at all tested doses (type 1: 75.5% vs 35.9% at 9 g, 66.9% vs 27.9% at 7.5 g, and 39.9% vs 7.8% at 6 g; all P < .001). Sleep latency was also improved compared with placebo, as measured with the Maintenance of Wakefulness Test; at the 9-g dose, the least squares mean difference was 6.0 minutes (P < .001) for patients with type 1 narcolepsy and 6.3 minutes (P < .05) for type 2. Avadel is currently recruiting patients for RESTORE, a long-term safety and tolerability study (NCT04451668) of FT218 in patients who are oxybate therapy naive or are currently taking either FT218 or a twice-nightly oxybate therapy.

Therapeutic strategies that address the underlying cause of narcolepsy, rather than simply managing symptoms, are desperately needed. Medically appropriate use of sodium oxybate is generally considered safe, with minimal risk of serious AEs; however, there have been reports of addiction, withdrawal syndrome, coma, and even death following abuse of illicit forms of GHB. Systematic studies of the genetic landscape of narcolepsy could inform the development of innovative treatments based on gene therapy or stem cells.

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For a full list of references, see the article on NeurologyLive.com.
POWERFUL MIGRAINE PREVENTION STARTS TODAY

VYEPTI is indicated for the preventive treatment of migraine in adults.

Help your patients meet their migraine-free potential today with one 30-minute treatment every 3 months.
PRIMARY ENDPOINT:
After the first dose, VYEPTI 100 mg and 300 mg reduced mean monthly migraine days by 7.7 and 8.2, respectively, vs. 5.6 with placebo (Months 1-3; baseline: ~16.1 mean MMD; p<0.001 vs. placebo; analysis of covariance model used to test for difference between treatment groups).

IN PATIENTS WITH ≥15 MHD OF WHICH ≥8 WERE MIGRAINE DAYS
VYEPTI PROVIDES MIGRAINE PREVENTION DESIGNED TO BE:

**FAST**
EARLY BENEFIT SEEN WITHIN THE FIRST 7 DAYS, AND AS SOON AS DAY 1 POST-INFUSION

Study design: This study was a parallel group, double-blind, placebo-controlled global trial to evaluate the efficacy and safety of VYEPTI for the preventive treatment of chronic migraine in adults. A total of 1,072 patients were randomized and received placebo (n=366), VYEPTI 100 mg (n=356), or VYEPTI 300 mg (n=350) every 3 months for 6 months. The efficacy and safety of VYEPTI for the preventive treatment of episodic migraine in adults was studied in PROMISE-1. For more information, please see the Prescribing Information.

VYEPTI 100 mg is the recommended dose. Some patients may benefit from the available and approved 300 mg dose. For more information on the 300 mg data, please see the Prescribing Information.

**POWERFUL**
~27% OF PATIENTS ON VYEPTI EXPERIENCED AT LEAST 75% FEWER MIGRAINE DAYS DURING MONTHS 1-3*

75% responder rate was defined as a subject achieving ≥75% reduction from baseline in migraine days for each month within the 3-month interval.

* One month was defined as 28 consecutive days.
† p<0.001 vs. placebo, stratified Cochran-Mantel-Haenszel test used for statistical analysis.

**SUSTAINED**
TREATMENT BENEFIT MAINTAINED THROUGH MONTH 6

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
VYEPTI is contraindicated in patients with serious hypersensitivity to eptinezumab-jjmr or to any of the excipients. Reactions have included angioedema.

WARNINGS AND PRECAUTIONS
Hypersensitivity reactions: Hypersensitivity reactions, including angioedema, urticaria, facial flushing, and rash, have occurred with VYEPTI in clinical trials. Most hypersensitivity reactions occurred during infusion and were not serious, but often led to discontinuation or required treatment. Serious hypersensitivity reactions may occur. If a hypersensitivity reaction occurs, consider discontinuing VYEPTI, and institute appropriate therapy.

ADVERSE REACTIONS
The most common adverse reactions (≥2% and at least 2% or greater than placebo) in the clinical trials for the preventive treatment of migraine were nasopharyngitis and hypersensitivity.

Please see Brief Summary of full Prescribing Information on the following page.

Reference:
VYEPTI Prescribing Information, Lundbeck Seattle BioPharmaceuticals, Inc.
VYEPTI™ (eptinezumab-jjmr) injection, for intravenous use

Brief Summary of Prescribing Information

(See package insert for full Prescribing Information or visit www.vyepiti.com)

Rx Only

INDICATIONS AND USAGE – VYEPTI™ (eptinezumab-jjmr) is indicated for the preventive treatment of migraine in adults.

CONTRAINDICATIONS – VYEPTI is contraindicated in patients with serious hypersensitivity to eptinezumab-jjmr or to any of the excipients in VYEPTI.

WARNINGS AND PRECAUTIONS – Hypersensitivity Reactions: Hypersensitivity reactions, including angioedema, urticaria, facial flushing, and rash, have occurred with VYEPTI in clinical trials. Most hypersensitivity reactions occurred during infusion and were not serious, but often led to discontinuation or required treatment. Serious hypersensitivity reactions may occur. If a hypersensitivity reaction occurs, consider discontinuing VYEPTI, and institute appropriate therapy [see Contraindications and Patient Counseling Information in full PI].

ADVERSE REACTIONS – 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 VYEPTI was evaluated in 2076 patients with migraine who received at least one dose of VYEPTI, representing 1615 patient-years of exposure; of these, 1524 patients were exposed to 100 mg or 300 mg. Across all doses, 1872 patients were exposed for at least 6 months and 391 patients were exposed for 12 months. In the placebo-controlled clinical studies (Study 1 and Study 2) of 1372 patients, 579 patients received at least one dose of VYEPTI 100 mg, 574 patients received at least one dose of VYEPTI 300 mg, and 588 patients received placebo [see Clinical Studies in full PI]. Approximately 86% were female, 89% were white, and the mean age was 40.4 years at study entry. The most common incidence (at least 2% and at least 2% greater than placebo) adverse reactions in the clinical trials for the preventive treatment of migraine were nasopharyngitis and hyperventilation.

Table 1 summarizes the adverse reactions that occurred during Study 1 and Study 2.

Table 1. Adverse Reactions Occurring with an Incidence of at Least 2% for VYEPTI and at Least 2% Greater than Placebo in Studies 1 and 2

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>VYEPTI 100 mg N=579 %</th>
<th>VYEPTI 300 mg N=574 %</th>
<th>Placebo N=588 %</th>
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<td>8</td>
<td>6</td>
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</tbody>
</table>

*Hypersensitivity reactions include multiple related adverse event terms, such as hyperventilation, pruritus, and flushing/hot flush that occurred on the day of dosing.

In Study 1 and Study 2, 1.9% of patients treated with VYEPTI discontinued treatment because of adverse reactions [see Warnings and Precautions in full PI].

IMMUNOGENICITY – As with all therapeutic proteins, 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 eptinezumab-jjmr in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. In patients receiving VYEPTI 100 mg or 300 mg every 3 months, the incidence of anti-eptinezumab-jjmr antibody development in Study 1 (up to 56 weeks) was 20.6% (92/447), and 41.3% (38/92) of those patients developed anti-eptinezumab-jjmr neutralizing antibodies. In Study 2 (up to 32 weeks), the incidence of anti-eptinezumab-jjmr antibody development was 18.3% (129/706), and 34.9% (45/129) of those patients developed anti-eptinezumab-jjmr neutralizing antibodies. In an open-label study with 84 weeks of treatment, 18% (23/128) of patients developed anti-eptinezumab-jjmr antibodies, and 39% (9/23) of those patients developed anti-eptinezumab-jjmr neutralizing antibodies. Although the results from both studies showed no clear evidence of an impact from development of anti-eptinezumab-jjmr antibodies, including neutralizing antibodies, on the safety and efficacy profiles of VYEPTI, the available data are too limited to make definitive conclusions.

USE IN SPECIFIC POPULATIONS – Pregnancy: Risk Summary – There are no adequate data on developmental risks associated with the use of VYEPTI in pregnant women. No adverse developmental effects were observed following administration of eptinezumab-jjmr to pregnant animals at doses greater than those used clinically [see Animal Data below]. In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively. The estimated rate of major birth defects (2.2%-2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations – Disease-Associated Maternal and/or Embryo/Fetal Risk: Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Data – Animal Data: When eptinezumab-jjmr (0, 75, or 150 mg/kg) was administered weekly to female rats and rabbits by intravenous injection throughout organogenesis, no adverse effects on embryofetal development were observed. The higher dose tested (150 mg/kg) is 30 times the maximum recommended human dose (MRHD) of 300 mg, on a body weight basis (mg/kg). When eptinezumab-jjmr (0, 75, or 150 mg/kg) was administered weekly to female rats throughout pregnancy and lactation, no adverse effects on pre- and postnatal development were observed. The higher dose tested (150 mg/kg) is 30 times the MRHD, on a mg/kg basis.

Lactation: There are no data on the presence of eptinezumab-jjmr 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 VYEPTI and any potential adverse effects on the breastfed infant from VYEPTI or from the underlying maternal condition.

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

Geriatric Use: Clinical studies of VYEPTI did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

Specific Populations: A population pharmacokinetic analysis assessing the effects of age, race, sex, and body weight did not suggest any clinically significant impact of these covariates on eptinezumab exposures.

Renal and Hepatic Impairment: No dedicated studies were conducted to assess the effects of renal or hepatic impairment on the pharmacokinetics of eptinezumab-jjmr. However, hepatic or renal impairment is not expected to affect the pharmacokinetics of eptinezumab-jjmr. A population pharmacokinetic analysis of integrated data from eptinezumab-jjmr clinical studies did not reveal clinically significant impact on pharmacokinetics of patients with hepatic or renal impairment.

Drug Interaction Studies: P450 Enzymes – Eptinezumab-jjmr is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Sumatriptan – The co-administration of a single dose of 300 mg eptinezumab-jjmr administered as an intravenous infusion (over a period of 1 hour ± 15 min) with a single dose of 6 mg sumatriptan administered subcutaneously did not significantly influence the pharmacokinetics of eptinezumab-jjmr or sumatriptan.

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Recent Breakthroughs in the Treatment of Alzheimer Disease

This NeurologyLive® Peers & Perspectives series features experts in the diagnosis and treatment of Alzheimer disease discussing the recent approval of aducanumab, its implications for Alzheimer disease, and other promising therapies and diagnostic technologies in development.

BRINGING EFFECTIVE TREATMENTS for Alzheimer disease (AD) from clinical development programs into the hands of clinicians has been an ongoing challenge that neurologists and geriatricians, among others, are all too familiar with. This is in part why the FDA approval of aducanumab (Aduhelm; Biogen) in June 2021 brought so much discussion to the field. Many viewed the approval as a major step toward breaking through the barrier that has prevented so many other promising agents from making it to market, while others questioned the clinical effectiveness of the drug based on its somewhat shaky supporting data.

Regardless, aducanumab’s approval was undeniably a landmark decision by the regulatory agency and one that will likely have lasting effects in the months—and perhaps years—to come. After some clarity was brought by the FDA in July 2021 to its indication about the proper patient population it can treat, some of the conversations in the field have shifted toward the ripples that the FDA decision might cause.

To find out about the possible consequences of this approval on the field of AD care, a recent NeurologyLive® Peers & Perspectives series brought together Richard S. Isaacson, MD, director, Weill Cornell Memory Disorders Program and director, Alzheimer’s Prevention Clinic, and director, Neurology Residency Training Program, Weill Cornell Medical College/NewYork-Presbyterian Hospital; and Marc E. Agronin, MD, senior vice president, Behavioral Health, and chief medical officer, MIND Institute, Miami Jewish Health. The pair sought to parse out the impact this decision may have, not only on the care of patients with AD, but also on the overall treatment landscape.

**Drugs in Development**

In the weeks since aducanumab was approved, a few other agents in the pipeline have been granted breakthrough designations by the FDA, namely, Eli Lilly’s donanemab—an antibody that targets a modified form of amyloid-β (Aβ) called N3p—and Biogen’s lecanemab—another anti-Aβ protofibril antibody, formally known as BAN2401. Isaacson pointed out that both agents are being evaluated in AD dementia and mild cognitive impairment and are headed to phase 3 studies, and mentioned galantamine, a cholinesterase inhibitor that was shown to potentially slow cognitive decline in AD earlier this year. Isaacson began by inquiring about these other agents, specifically pondering what effects this approval may have on the FDA’s willingness to approve investigational therapies that operate similarly to aducanumab.

“Yes, [I think the likelihood of success is increased for those agents], and I would throw into the mix antitau treatments also that are being looked at,” Agronin said. “This is a question that’s been raised, given the FDA’s approach here: Is this going to set a precedent to change the bar in terms of other treatments? I’ve been to some FDA review committees and it’s a tough environment for any treatment for AD. Almost everything has failed through it and with good reason: Either the data are there or they are not there. We need data and we need studies.”

Agronin continued by noting the impact that this approval, the first of its kind, may have on clinical trial participation in a negative way. He explained that now there may be less interest in participation because of the demand to get access to treatment, and as the screening process is very rigorous for the trials being conducted in AD, participation in studies can be almost burdensome for patients. “I have some studies where it’s a 2- or 3-month process of multiple scans, multiple scales, and someone is asking themselves, ‘Am I going to go through that process for 2 years to be on potential placebo? I can walk down the street and get this infusion,’” Agronin said.

These possible complications have led many to question the design of clinical trials in AD, and Agronin raised several questions: Do they need to be shorter in length? Do they need to move more quickly to open-label stages? Should aducanumab be an active comparator? All these questions, despite currently lacking [ ]
answers, will likely weigh on those working as investigators in the field. The main concern for Agronin and Isaacson is the possible impact on research in AD.

But the rippling effect doesn’t stop at research. Much of the discussion on aducanumab in the weeks following its approval has centered around access to the therapy. Some, such as the Institute for Clinical and Economic Review, have published reports that its current list price of $56,000 annually far exceeds the cost-benefit ratio. On top of this, many questions remain to be answered about coverage for patients, both from insurers and from Medicare.

“My sense is—I’m trying to be very optimistic here—that I think this is going to be a very gradual rollout. I think what we’re going to see both from clinicians and payers is that there’s going to be a pretty high bar to qualify for the treatment to get payment for it,” Agronin said. “Sure, some people are going to walk in and just want to pay cash for this. I don’t think that’s going to be the majority. I think that will be few and far between, so I think it’s going to be done in a very measured way.”

Ultimately, Agronin and Isaacson agreed that perhaps the weightiest challenge for the physician community at this point is coming to consensus. Agronin noted that with the varying concerns being raised by colleagues in the field, getting clinicians across the US on the same page about the therapy’s potential benefit, proper indication, and clinical use will be of paramount importance going forward. Its importance cannot be overstated, according to Isaacson, particularly as it pertains to ensuring effective communication with patients.

“Patients do what they want to do, and [its approval] even opens up the door to [a scenario where] someone is on aducanumab, they’re in another clinical trial, and [drugs] could be mixing; there are lots of potential issues there that we need to have very frank conversations with patients about,” Isaacson explained. “I think that is going to be very few and far between—at least I hope it would be. However, there are studies being planned for that now. Obviously, if you’re on an antiamyloid drug in a clinical trial, you really should not be on the antiamyloid drug in practice; that’s easy. But what about an antitau drug in a clinical trial; can you be on the amyloid drug in practice? That probably mixes things up and confuses things.”

As an example, Isaacson pointed to an ongoing trial with semaglutide (Ozempic; Novo Nordisk), a glucagon-like peptide-1 (GLP-1)–targeted drug approved for the treatment of diabetes. The study, dubbed EVOKE (NCT04777396), is a phase 3 study aiming to enroll more than 3700 individuals to assess the drug’s impact on cognition and AD progression over a 2-year period.

“That study, to my understanding, allows someone to be on an antiamyloid drug. There may be some studies that people could go into and participate in as well as being on aducanumab. How do you track that? How do you analyze for that? Obviously, it’s a randomized trial, so hopefully some of that will shake out, but it really adds just another level of statistical complexity, real-world complexity, and recruitment complexity when you have a drug like this available in the market,” Isaacson said.

Agronin pointed to similar and current confounding effects that are experienced in trials that include individuals on acetylcholinesterase inhibitors and memantine, noting that to Isaacson’s point, aducanumab may join the list as an acceptable background therapy for trial participants.

In addition to ridding the brain of Aß plaques, the addition of these investigational agents on top of approved therapy in trials may be the key to slowing the disease course. As Agronin put it, clearly more is needed than simply targeting a single pathology of AD, but it is important that studies that are looking at other modalities are not compromised along the way.

“I’m seeing over time—I would say across the board for not just Alzheimer studies but other clinical trials—there is a greater allowance for other modalities being used simultaneously,” Agronin explained. “Obviously, someone can’t be in more than 1 clinical trial at the same time, but I think realistically, that is probably going to become more the reality that either the studies allow these other treatments or they’re really going to have a hard time enrolling.”
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BTK Inhibitor Fenebrutinib Aims to Tackle Progressive MS in FENtrepid Trial

The agent’s safety profile has been studied in more than 1200 individuals to date across several inflammatory diseases, with data indicating that the high selectivity of fenebrutinib may limit off-target effects.

By Marco Meglio

IN SEPTEMBER 2020, Roche announced it was initiating a new phase 3 clinical trial program for fenebrutinib, an investigational oral Bruton tyrosine kinase (BTK) inhibitor for the treatment of relapsing multiple sclerosis (RMS) and primary progressive MS (PPMS). The program included 2 identical phase 3 trials in RMS, FENhance 1 (NCT04586023) and FENhance 2 (NCT04586010), and a separate phase 3 trial in PPMS, FENtrepid (NCT04544449).¹

FENtrepid, a multicenter, double-blind, double-dummy, parallel-group study, is expected to enroll up to 946 patients with PPMS aged 18 to 65 years. Eligible participants will be randomly assigned 1:1 to either daily oral fenebrutinib or placebo or intravenous ocrelizumab (Ocrevus; Genentech) for 120 weeks (FIGURE). An open-label extension trial may follow FENtrepid, depending on the observed benefits.

Investigators will use time to onset of composite 12-week confirmed disability progression (CDP) as the primary outcome measure, whereas time to onset of composite 24-week CDP, percentage change in total brain volume assessed by MRI, and change from baseline in participant-reported physical impacts of MS will all be among secondary end points observed.

Alexandra Goodyear, MD, MS, global development lead, Roche, told NeurologyLive®, “With a BTK inhibitor acting on the myeloid cells, we’re hopeful that we can act on the chronic inflammatory processes that seem to be underlying disability progression. Disability progression remains the key unmet need within the MS community.”

“It’s the dual mechanism of action that is really exciting. People have asked, ‘How do we address the compartmentalized inflammation that is pointing to underlying disability progression?’ BTK inhibitors are hitting all the B cells and myeloid cells that are acting on innate immunity.”

Fenebrutinib is unique because it is a noncovalent and reversible BTK inhibitor compared with other agents, such as ibrutinib (Imbruvica; AbbVie/Janssen), tolebrutinib (Sanofi), and evobrutinib (EMD Serono), which are all covalent and irreversible.

Early clinical safety data thus far have confirmed the high selectivity of fenebrutinib compared with other BTK inhibitors. The reasons for its high selectivity stem from its binding mode: the agent binds orthogonally and selects a unique pocket. In whole blood assays, fenebrutinib potently inhibits myeloid and B-cell activation, shown by half-maximal inhibitory concentrations of 8 nM and 31 nM, respectively.²

The rate at which a drug dissociates from its target can influence its duration of action and efficacy. Data also showed that although fenebrutinib’s residence time in vivo may be less than 18 hours, its slow dissociation from BTK may positively influence efficacy. Investigators also concluded that its preclinical pharmacokinetic characteristics are favorable, indicating the potential for once-daily oral dosing.

A group of investigators, including Goodyear, presented research at MSVirtual2020, the 8th Joint ECTRIMS-ACTIMS Meeting, held in September 2020, which highlighted the drug’s mechanisms and compared them with those of other BTK inhibitors. At the end of the presentation, the study authors concluded that fenebrutinib may be safer than less selective, covalent BTK inhibitors and that it has best-in-class potential in MS.

Fenebrutinib’s safety profile was further examined and confirmed through an analysis that included data from phase 2 randomized, controlled clinical trials and open-label extensions in diverse autoimmune indications such as rheumatoid arthritis, systemic lupus erythematosus, and chronic spontaneous urticaria. Safety assessments included adverse events (AEs), laboratory results, electrocardiogram results, and vital signs.³

A total of 972 patients were exposed to fenebrutinib at the highest dose (200 mg), 493 of whom were exposed for at least 48 weeks. All told, AEs reported in at least 5% of fenebrutinib-treated patients in randomized controlled trials (n = 299) were nasopharyngitis (6%), nausea (5.7%), and headache (5.4%). No patients experienced atrial or ventricular tachyarrhythmias. Bleeding or bruising was reported in 23 patients (7.7%) receiving fenebrutinib vs 3.2% receiving placebo, with no cases of major hemorrhage reported.

All 3 of the phase 3 trials have currently been initiated. Roche noted that it is too early for updates on when potential data readouts may come. “Our goal is that we can stop disability progression, not just for primary progressive patients but for all patients with MS, [thus] recognizing that this affects all patients from the beginning of their disease,” Goodyear said.

For a full list of references, see the article on NeurologyLive.com.
STROKE CONTINUES TO BE THE fifth-leading cause of death in the United States.1 High blood pressure, diet, physical inactivity, smoking, and abdominal obesity were the top 5 risk factors associated with ischemic and hemorrhagic stroke incidence observed in the INTERSTROKE study.2 Targeting multiple risk factors has a combined benefit for secondary prevention—medications combined with diet modification and exercise can result in an 80% cumulative risk reduction in recurrent vascular events, according to findings from Hackam et al.3

The recent American Heart Association (AHA)/American Stroke Association guideline on secondary stroke prevention provides comprehensive practical guidance for prevention of recurrent ischemic stroke and transient ischemic attack (TIA).4 The TABLE provides a few of the major practice changes based on the guidelines.

**TABLE.** Practice Changes Based on the 2021 AHA/ASA Secondary Stroke Prevention Guidelines

<table>
<thead>
<tr>
<th>HOW DOES THIS CHANGE MY PRACTICE?</th>
<th>STUDY REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>If LDL-C remains ≥ 70 mg/dL on maximally tolerated statin therapy, add ezetimibe and then a PCSK9 inhibitor.</td>
<td>IMPROVE-IT (NCT00202878)</td>
</tr>
<tr>
<td>Check fasting triglycerides levels, and if 135-499 mg/dL with no contraindications to treatment, add IPE 2 g bid to statin.</td>
<td>REDUCE-IT (NCT01492361)</td>
</tr>
<tr>
<td>Check for insulin resistance in patients with HbA1c level &lt; 7.0%, and if no contraindications to treatment, add pioglitazone.</td>
<td>IRIS (NCT00091949)</td>
</tr>
<tr>
<td>In patients who qualify for DAPT because of minor stroke/high-risk TIA/intracranial atherosclerosis and cannot be treated with clopidogrel, use ticagrelor or cilostazol instead.</td>
<td>THALES (NCT03354429), TOSS (NCT00130039)</td>
</tr>
</tbody>
</table>

AHA, American Heart Association; ASA, American Stroke Association; bid, twice a day; DAPT, dual antiplatelet therapy; HbA1c, glycated hemoglobin A1c; IPE, icosapent ethyl; LDL-C, low-density lipoprotein cholesterol; TIA, transient ischemic attack.

**Physical Inactivity**

The 2014 guidelines recommended that stroke survivors aim to achieve 40-minute sessions of moderate to vigorous intensity exercise at least 3 to 4 times a week.5 Emerging data from the SAMMPRIS trial (NCT00576693) have revealed benefit of intermittent, 10-minute bouts of moderate physical activity (sufficient to noticeably raise heart rate, like walking briskly) up to 4 times a week or 20-minute bouts of vigorous activity (like jogging) up to twice a week.6 This has now been added as a guideline recommendation for patients with stroke who are unable to achieve the prior recommendations.

**Substance Use**

With the advent of new psychoactive substances and the legalization of marijuana in many states, recent studies have demonstrated an increased association of substance use with strokes.7-10 For patients with stroke or TIA who use stimulants (such as amphetamines, amphetamine derivatives, cocaine, or khat) and for patients with infective endocarditis with active intravenous drug use, health care providers should note that this behavior is a health risk and counsel them to stop. Although cannabis is not specifically mentioned in the above guideline, the CDC identified that young adults (aged 18-44 years) with recent cannabis use have higher odds of stroke compared with nonusers, which increases with frequent cannabis use (> 10 days/month).11

**Hypertension**

In 2017, the AHA/American College of Cardiology hypertension guideline defined hypertension as blood pressure consistently greater than 130/80 mm Hg.12 An independent Cochrane analysis and a large meta-analysis provided compelling evidence that neurologically.
stable patients with cerebrovascular disease also benefit from a blood pressure goal of less than 130/80 mm Hg.\textsuperscript{13,14} Target blood pressure for stroke prevention is now more aligned with cardiovascular targets.\textsuperscript{4} Current guidelines recommend a goal of less than 130/80 mm Hg in patients with recent stroke or TIA for prevention of recurrent events.

### Hyperlipidemia and Hypertriglyceridemia

A secondary analysis of the IMPROVE-IT trial (NCT00202878) found a significantly lower risk of ischemic stroke with ezetimibe treatment (in addition to simvastatin) among patients with previous myocardial infarction (MI).\textsuperscript{15} Ezetimibe use before initiating a PCSK9 inhibitor is recommended because ezetimibe is available as a generic drug and has proven safety.\textsuperscript{16} This guideline strongly recommends that high-risk patients with atherosclerotic cardiovascular disease receive high-intensity statin therapy and that if low-density lipoprotein cholesterol (LDL-C) level remains greater than or equal to 70 mg/dL on maximally tolerated statin therapy, it may be reasonable to add ezetimibe and then a PCSK9 inhibitor if necessary.

The REDUCE-IT trial (NCT01492361) revealed a 25% reduction in the primary end point of major adverse cardiovascular events in patients who were randomized to icosapent ethyl (IPE) 2 g twice daily plus statin therapy.\textsuperscript{17} A new recommendation is to include treatment with IPE in patients with ischemic stroke or TIA, with a fasting triglyceride level of 135 to 499 mg/dL and an LDL-C level of 41 to 100 mg/dL, on moderate or high-intensity statin therapy, with a glycated hemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) level of less than 10% and no history of pancreatitis, atrial fibrillation (AF), or severe heart failure to reduce risk of recurrent stroke.

### Diabetes Mellitus

Although insulin resistance is not routinely evaluated in patients with stroke/TIA, the new guidelines mention that in patients 6 months or less after TIA or ischemic stroke with insulin resistance, HbA\textsubscript{1c} level less than 7.0%, and without heart failure or bladder cancer, treatment with pioglitazone may be considered to prevent recurrent stroke. This is based on results of the IRIS trial (NCT00091949), which examined the effect of pioglitazone compared with placebo among patients without diabetes who had a recent ischemic stroke and insulin resistance. After a mean of 3.8 years, a relative risk reduction of 24.0% was noted in recurrent stroke or MI compared with 11.8% among placebo recipients and 9.0% among pioglitazone recipients.\textsuperscript{18}

### Intracranial Atherosclerosis

The THALES trial (NCT03354429) demonstrated a reduced risk of recurrent stroke or death at 30 days among patients with greater than or equal to 30% intracranial stenosis ipsilateral to the ischemic event who were treated with ticagrelor and aspirin compared with aspirin alone (9.9% in ticagrelor + aspirin vs 15.2% aspirin alone).\textsuperscript{19} In this subgroup of patients with recent (within 24 hours) minor stroke or high-risk TIA and concomitant ipsilateral more than 30% stenosis of a major intracranial artery, the addition of ticagrelor 90 mg twice a day to aspirin for up to 30 days might be considered to further reduce recurrent stroke risk.

In patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the addition of cilostazol 200 mg/day to aspirin or clopidogrel might be considered to reduce recurrent stroke risk. This new recommendation is based on the TOSS and TOSS-2 (NCT00130039) trials, which revealed that cilostazol plus aspirin was as safe as aspirin alone or clopidogrel plus aspirin with no added benefit for stroke prevention in this subgroup.\textsuperscript{20,21} Cilostazol can hence be considered especially in patients who are unable to respond to or tolerate clopidogrel.

### Atrial Fibrillation

The improved safety profile of direct oral anticoagulants (DOACs) with noninferior thromboembolic risk has led to the preferential use of a DOAC over warfarin.\textsuperscript{22} However, a subset of the patient population is still unable to tolerate any anticoagulation because of increased bleeding risk. Left atrial appendage occluders such as the Watchman device have demonstrated nonsignificant numerically greater thrombotic risk with the device but lower bleeding risk and overall net benefit in recent trials.\textsuperscript{23} This evidence has led to a new recommendation for consideration of percutaneous closure of the left atrial appendage with the Watchman device to reduce the chance of recurrent stroke and bleeding in patients with stroke or TIA in the setting of nonvalvular AF who have contraindications for lifelong anticoagulation but can tolerate at least 45 days of blood thinners.

All DOAC medications are renally cleared, increasing the risk of drug accumulation and bleeding events in patients with renal failure.\textsuperscript{24} Although overall data are limited, a large retrospective study matched patients with AF on dialysis who took apixaban against patients taking warfarin and found a 28% lower rate of bleeding events in those taking apixaban,\textsuperscript{3} supporting its use as an alternative choice for anticoagulation in patients with AF on dialysis.

### Patent Foramen Ovale Closure

Several studies have evaluated secondary stroke prevention of patent foramen ovale closure since the previous guideline in 2014.\textsuperscript{25-28} It is now considered reasonable to percutaneously close patent foramen ovale in patients who meet the following criteria: aged 18 to 60 years, nonlacunar stroke, absence of other identified cause, and a high-risk patent foramen ovale (larger shunt size, atrial septal aneurysm).

### Embolic Stroke of Undetermined Source

The NAVIGATE ESUS (NCT02313909) and RE-SPECT ESUS (NCT02239120) randomized trials found no reduction in secondary stroke risk among patients with ischemic stroke or TIA who were treated with a direct oral anticoagulant compared with antiplatelets.\textsuperscript{29,30} Hence, in patients with embolic stroke of undetermined source, treatment with direct oral anticoagulants is not recommended to reduce the risk of secondary stroke.

The guideline also has added sections on specific rare disorders like antiphospholipid syndrome, hypercoagulable states, central nervous system and infectious vasculitis, carotid webs, fibromuscular dysplasia, and genetic disorders. Although guidelines are intended to define practices meeting the needs of patients in most circumstances, they should not replace clinical judgment; furthermore, the recommendations should be considered in the context of individual patient laboratory values, preferences, and associated conditions.\textsuperscript{4}
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Differentiating Tardive Dyskinesia From Similar Drug-Induced Movement Disorders

Tardive dyskinesia can present many challenges in its treatment and can be difficult to differentiate from similar disorders.

By Laxman Bahroo, DO; and Jonathan Isaacson, MD

THE DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, FIFTH EDITION, defines tardive dyskinseia (TD) as involuntary choreiform or athetoid movements caused by exposure to dopamine receptor–blocking agents that persist beyond 4 to 8 weeks. TD displays heterogeneity in phenomenology and can present as dystonia, akathisia, stereotypy, tics, myoclonus, tremor, or chorea. Typically, it manifests as involuntary stereotypic movements of the oral-buccal-lingual area with such movements as lip smacking, facial grimacing, and tongue movement.1 TD can also manifest with repetitive movements of the limbs, including foot tapping, complex stereotypical finger and toe movements, and repetitive rocking and swaying movements of the trunk.2 TD may also involve the laryngeal, pharyngeal, and diaphragmatic muscles.3

It is important to understand that TD is a separate entity from extrapyramidal symptoms (EPSs) and neuroleptic-induced parkinsonism. Parkinsonism can occur at any time during exposure to a neuroleptic, though removing or reducing the agent may improve EPSs and parkinsonism. In TD, the removal of the agent rarely completely reverses symptoms and may unmask or precipitate symptoms.4

Clinical Impact and Causes of TD

The impact of TD is vast. In a meta-analysis of patients on first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), it was found that 25.3% of patients suffered from TD.5 Although rates were higher in FGA at 30%, SGAs still had a prevalence of 20.7%. This is further pronounced given the higher frequency of SGA use in recent years for severe depression, bipolar disorder, and behavioral disturbances in elderly patients.

TD also has significant consequences on quality of life and daily functioning, including impaired gait and posture, gastrointestinal function, disrupted speech, respiration, and psychosocial complications such as occupational impairment, social
stigmatization, depression, and even suicide. Although prior studies were isolated to patients on FGAs or with underlying schizophrenia, the expanded and broader use of antipsychotics to include patients who are highly functional will likely result in the distressing impact on quality of life of TD to be even more pronounced. In the RE-Kinect trial (NCT03062033), it was shown that 75.5% of patients in the possible TD cohort (n = 204) were aware of their TD symptoms, and found that even mild symptoms can have a large impact on their quality of life and ability to participate in daily activities such as the ability to take care of themselves, socialize, be productive, and even talk and eat.

Long-term exposure to first- and second-generation neuroleptics is the most common cause of TD. Less common causes are the use antiemetic drugs, selective serotonin reuptake inhibitors, lithium, and tricyclic antidepressants. Factors that affect the development of TD are age, duration of illness and cumulative dose, potency of neuroleptic, female sex, prior brain damage, concurrent mood disorders, substance use, and gene polymorphisms.

Common Misconceptions
There are many misconceptions about TD. Although EPS resolves with discontinuation of neuroleptics, TD rarely resolves with removal of the agent. The complete reversibility of symptoms was between 2% and 20% of patients after discontinuing the agent. Although FGAs certainly have the highest risk, SGAs also carry a significant risk of TD. The expanded use of SGAs for depression, bipolar disorder, and delirium in the elderly population has increased the prevalence of TD in recent years. TD is often minimalized as unbothersome, but as the RE-Kinect trial findings illustrate, the effect of TD on quality of life and daily living can be intrusive and distressing.

Treatment for TD
Since TD’s discovery, treatment has been a challenge for clinicians. Attempts at decreasing the dose or removing the offending agent are fraught with not only the worsening of patients’ underlying psychiatric disorder, but also futility, as removal of the medication rarely cures TD. Furthermore, complete removal of the dopamine receptor blocking agent (DRBA) typically acutely worsens TD symptoms, but continuation of the DRBA may potentially cause a worsening of symptoms. These challenges have led to an unmet need for medications that treat TD symptoms.

VMAT2 Inhibitors
Reversible vesicular monoamine transporter-2 (VMAT2) inhibitors work by blocking a neurotransmitter transporter that packages dopamine, noradrenaline, serotonin, and histamine into presynaptic vesicles for release into the synaptic cleft. By blocking the transporter, less of the neurotransmitter will be packaged into the presynaptic vesicle, and less neurotransmitter will act on the postsynaptic receptor.

Tetrabenazine was first approved for Huntington disease (HD) in 2008 to treat chorea and hyperkinetic movements. Its use was later expanded to include off-label treatment of other hyperkinetic movement disorders. Tetrabenazine is a high-affinity, reversible VMAT2 inhibitor. The half-life of tetrabenazine is short, the agent therefore...
requires thrice-daily dosing. It has been shown to be effective and well tolerated in multiple studies but is somewhat limited by its adverse effects (AEs) including somnolence, parkinsonism, and severe depression and suicidality.\textsuperscript{15}

Deutetrabenazine (Austedo; Teva) is another available reversible VMAT2 inhibitor. Deutetrabenazine is very similar to tetrabenazine, with the main difference being the deuterium replacing the hydrogen ion in the agent. The deuterium results in a slowed metabolic clearance and lower maximum concentration value. This results in favorable a pharmacokinetic profile, with a halflife of 9 to 10 hours and twice-daily dosing. The medication must also be taken with food. Deutetrabenazine was approved by the FDA in 2017 and was the second approved therapy for both HD and TD.

The AIM-TD study (NCT02291861) included 298 patients with moderate to severe TD and assessed Abnormal Involuntary Movement Scale (AIMS) scores at 12 weeks in those randomized to receive at least 1 dose of placebo (n = 74), deutetrabenazine 12 mg/day (n = 75), 24 mg/day (n = 74), or 36 mg/day (n = 75). The study reported a statistically significant change in AIMS score from baseline to week 12 of −3.3 points (standard error, [SE], 0.42) in the deutetrabenazine 36-mg/day group, −3.2 points (SE, 0.45) in the 24-mg/day group, and −2.1 points (SE, 0.42) in the 12-mg/day group. This equated a treatment difference of −1.9 points (SE, 0.58; 95% CI −3.09 to −0.79; \(P = .001\)), −1.8 points (SE, 0.60; 95% CI −3.00 to −0.63; \(P = .003\)), and −0.7 points (SE, 0.57; 95% CI −1.84 to 0.42; \(P = .217\)), respectively, compared with −1.4 points (SE, 0.41) in the placebo group.\textsuperscript{16}

Another study, ARM-TD (NCT02195700), included 117 patients in a 12-week assessment compared with placebo in a randomized, double-blind, multicenter manner. In addition to AIMS, this study also evaluated Clinical Global Impression (CGI) and Patient Global Impression (PGI) scores. In ARM-TD, deutetrabenazine significantly reduced AIMS scores from baseline to week 12 compared with placebo, with the treatment arm seeing a change of −3.0 (SE, 0.45) and the placebo arm a change of −1.6 (SE, 0.46; \(P = .019\)). Treatment success on CGI (48.2% vs 40.4%) favored deutetrabenazine but was not significant.\textsuperscript{15} The most common AEs with this agent are headaches, somnolence, and parkinsonism.

Another option is valbenazine (Ingrezza; Neurocrine), a novel, highly selective reversible VMAT2 inhibitor. It consists of an α-enantiomer and 2 isomers, which all have VMAT2 binding. The half-life is 20 hours, which allows for once-daily dosing. It can be taken with or without food. Valbenazine was approved in 2017 and was the first FDA-approved therapy for TD. KINECT 3 (NCT02274558) was a phase 3 trial with 234 patients with TD randomized to placebo, 40-mg valbenazine, and 80-mg valbenazine for 6 weeks. The primary end point was change in AIMS score. AIMS score changed by −3.2 in the 80-mg valbenazine arm, −1.9 in 40-mg arm, compared with −0.1 in placebo arm (\(P < .001\)), corresponding to an effect size of 0.90. Common AEs include somnolence, akathisia, and dry mouth.\textsuperscript{18}

**Other Therapies**

Amantadine has long been used for its antiparkinsonism effects and has been expanded to include the treatment for patients with TD. It works by noncompetitive antagonism to N-methyl-D-aspartate acid receptors. It is postulated that it increases dopamine release and prevents reuptake.\textsuperscript{19} One 18-week, crossover, randomized controlled trial used amantadine 300 mg in addition to a neuroleptic and observed a 15% reduction in AIMS scores.\textsuperscript{20} Amantadine with a neuroleptic has level C evidence for the treatment of TD. Vitamin E has also been studied for the treatment of TD. It is postulated that its antioxidant properties may have an effect on the disease. Although, in one trial of 158 patients who were given 1600 IU of vitamin E compared with placebo, there was no difference in AIMS scores.\textsuperscript{21} In other class 2 and 3 studies there were reductions in AIMS scores ranging from 8.5% to 43% reduction of AIMS.\textsuperscript{22} Given these conflicting studies, there is currently insufficient data to determine the efficacy of vitamin E in TD.

Ginkgo biloba is a tree native to China used for centuries in traditional medicine. The leaves contain terpenoids and flavonoids, which have antioxidant properties. In one randomized controlled trial of 157 patients, individuals were given 240 mg of gingko or placebo. The AIMS scores improved by 2.13 in the gingko arm vs −0.10 in placebo.\textsuperscript{23} Gingko as such has level B evidence, deemed as probably useful, but data are limited.

Botulinum toxin A is an adjunct therapy for the treatment of TD. Botulinum toxin A has the most evidence for its use in focal TD. In a single-blind study with 12 patients, there was a nonsignificant reduction in orofacial movements with botulinum toxin B (\(P = .15\)). However, when controlling for medication changes, there was a significant reduction for patients on stable dose of antipsychotic (\(P = .035\)). Half (50%; \(n = 6\)) of patients preferred to continue treatment with botulinum toxin A.\textsuperscript{24} Other smaller case reports showed evidence of efficacy in persistent TD with tongue protrusion that improved with botulinum toxin A.\textsuperscript{25} Further studies are needed to better display efficacy.

**Clinical Takeaways and Conclusion**

TD has long been underrecognized and suboptimally treated, creating a challenge to adequately treat patients with this disorder. In 2017, the approval of valbenazine and deutetrabenazine revolutionized the treatment of TD. Both demonstrated safety, efficacy, and tolerability in clinical trials. Although these therapeutics are now available, diagnostic challenges still remain. The incidence of TD has grown in recent years and the trend is likely to continue given the widened indications for DRBAs. Obstacles, in terms of awareness, screening, and surveillance remain, but these new therapeutics offer a major key to enhancing the lives of thousands.\textsuperscript{26}
Deborah W. Brooks Is Named CEO of Michael J. Fox Foundation for Parkinson’s Research

The Michael J. Fox Foundation for Parkinson’s Research (MJFF) announced in May 2021 that Deborah W. Brooks, cofounder of the organization with Fox in 2000, would step up as CEO. Brooks will lead the company in its mission to identify a cure for Parkinson disease (PD) while providing support for those living with the disease. Todd Sherer, PhD, will move from his role as CEO to the newly created role of executive vice president, research strategy, employing his scientific and clinical background to further PD research and drug development initiatives. Additionally, Sohini Chowdhury was named deputy CEO, head of research, and will be tasked with leading plans for research and grant funding. According to Skip Irving, chairman of the MJFF board of directors, Brooks, Sherer, and Chowdhury have worked as a team for several years. In a statement, Irving added, “This transition reflects their continued unwavering resolve to do the most good for the millions living with PD.”

$10 Million in Additional Funding Is Announced for Parkinson Disease Research

The Parkinson’s Foundation announced additional research funding, in the amount of $10 million, to improve quality of life for those with Parkinson disease (PD). Funding will bolster the PD GENEration: Mapping the Future of Parkinson’s Disease program, which aims to expand clinical trial inclusion for those with PD within the Hispanic and Caribbean communities, both of which are historically underrepresented groups. James Beck, PhD, senior vice president and chief scientific officer of the foundation, noted in a statement that the “goal is to diversify the participants in the PD GENEration study so that we can accelerate clinical studies, improve Parkinson research and care and empower all people with Parkinson, regardless of their background.” An additional $2 million investment in community grants for the foundation provides for underserved PD communities, many of which have unmet needs.

Alliance Gives $1.7 Million to Fund Progressive MS Research

The International Progressive MS Alliance is providing 19 individual projects around the globe roughly $90,000 each to facilitate research into why multiple sclerosis (MS) progresses. Understanding what drives progression will aid in slowing or stopping progression; however, investigators are currently unaware of what directly drives this aspect of MS. Projects will explore different areas ranging from tau misfolding to the role of adenosine A2A receptor in the pathogenesis of progressive MS. A worldwide call for applications was made, with applicants reviewed by an international panel of MS experts. Projects from 13 different countries were eventually selected for 1 year of funding. Results from projects are anticipated to be reported in 2022, with funding starting later in 2021. Investigators anticipate gaining insight into why and how MS progresses, as well as identifying new therapeutic targets and resultant treatments.