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Addressing the Needs of a Growing Patient Population

EVEN BEFORE THE ONSET OF the COVID-19 pandemic, the medical field had been facing myriad unforeseen challenges that care team members have stepped up to address in times of great need. Although the field has pushed forward in light of these difficulties, another challenge has loomed in the background for the past several years: the physician shortage.

In neurology specifically, this has presented a rather large obstacle. Rising patient populations, which are projected to continue, have been paired with fewer physicians entering the field than needed to meet the demand for care. In response, large medical societies and institutions have begun to implement strategies to adjust to and overcome this challenge, although the problem persists. In this issue of NeurologyLive®, our cover story examines what is driving this physician shortage and the ongoing efforts to address it. Appearing on page 14, it includes insight from Jennifer Majersik, MD, MS, who coauthored a recent report that called for more attention to be paid to this problem.

Also in this issue is a look into the latest advances in gene-transfer therapy for neuromuscular disorders, a wide variety of which are in dire need of novel therapeutic approaches to complex pathologies. Gene therapy interventions hold great promise for many of these patient populations, and on page 28, Crystal M. Proud, MD, provides an update on the progress that has been made in developing these therapies.

Another complex disease for which the clinical community has long sought more effective therapies is Parkinson disease. Although levodopa has been a gold-standard mainstay of the care paradigm for half a century, the field has chased longer-lasting and better-performing therapies for some time now. Most recently, though, experts such as Adolfo Ramirez-Zamora, MD, have begun to reexamine how they view Parkinson disease, and on page 31, he explains how perspective has shifted to see it as a collective syndrome rather than a single disease process, and how improving patient classification can improve care in parallel.

The process of communicating medical advances to the public has been in the spotlight even more than usual in the past 2 years, around the response to COVID-19. However, the communication of changes to care standards on a physician level is similarly important, particularly in instances when guidelines are updated. On page 34, Daniel Ackerman, MD, FAAN, provides practical insight into the effective communication of updates in treatment processes to patients to prevent poor outcomes, especially in a time where patients believe they are more informed than ever and, yet, correct information can be difficult to identify.

As we strive to keep you abreast of the latest research and tools to improve your clinical practice, we always welcome your feedback. If you have any comments or thoughts about our coverage or would like to contribute to NeurologyLive®, please email Managing Editor Matt Hoffman at mhoffman@neurologylive.com.

Thank you for reading.
Mike Hennessy Jr
President and CEO, MJH Life Sciences®
Genetic Neurodegenerative Disorders: Close to a Symptom-Free Life?

By John Brandsema, MD

Breakthroughs in targeted genetic treatment have transformed medicine in recent years, with specialties such as neuromuscular neurology in the vanguard. In this issue of NeurologyLive®, Crystal M. Proud, MD, expertly outlines recent advances in neuromuscular care—with more promising approaches on the near horizon—and reviews some of the unanswered questions requiring further research now that it has become standard of care to alter genetic expression in our patients in the clinic.

Spinal muscular atrophy (SMA) is the first disease with an approved systemic in vivo gene therapy in the US, available since 2019. With onasemnogene abeparvovec-xioi (Zolgensma; Novartis) for survival motor neuron (SMN) gene transfer, as well as nusinersen (Spinraza; Biogen) in 2016 and risdiplam (Evyrsdi; Genentech) in 2020 as RNA-based therapies, there has been a transformative impact on SMA disease course over the past 5 years. Currently in the clinic, discussions that were once primarily of a palliative nature are focused rather on potential for minimum disease stabilization and often improved function with treatment. Real-world data on short- and long-term impact of all 3 approved SMA treatments continue to be collected.

Duchenne muscular dystrophy (DMD) also has had several recent genetically targeted therapy approvals. The conditional approval of eteplirsen (Exondys 51; Sarepta), an antisense oligonucleotide targeting skipping of exon 51, by the FDA in 2016 marked the first DMD-targeted therapy to receive a conditional approval in the US; after subsequent approval of exon 53 skipping with golodirsen (Vyondys 53; Sarepta) and viltolarsen (Viltelpso; NS Pharma) and exon 45 skipping with casimersen (Amondys 45; Sarepta) in 2021, approximately 25% to 30% of patients are eligible for exon-skipping treatments.1 As the size of the dystrophin gene precludes gene transfer with existing viral vector technology, programs are under way utilizing tailor-made versions incorporating the most critical regions for DMD protein function within the muscle fiber. A rise in genetically targeted treatment trials continues to hold promise for rarer and/or more heterogeneous genotypes and phenotypes; this powerful therapeutic option still has many unknowns about ideal timing of intervention, short- and long-term toxicities, and durability in the context of optimization.

Early diagnosis and referral for treatment are key in neurodegenerative disorders, as most reach an irreversible stage in affected tissues.2 The race of decline can be highly variable across the phenotypic spectrum, and approaches such as newborn screening, now in place for SMA in the majority of US births as well as in several other countries, lead to considerations about optimal timing of intervention based on available biomarkers; in SMA, genotype is the most well-established, and debate continues over timing of intervention for those with more than 4 SMN2 copies.3 Some who receive a diagnosis via screening and are seen immediately postnatally are symptomatic and do not have as robust a response to treatment, suggesting a wider spectrum of prenatal onset of motor neuron loss than had been appreciated in natural history studies. Prenatal therapies are also being studied preclinically. Precise and reliable biomarkers of disease onset and rate of progression in neurodegenerative disorders significantly aid treatment decisions but must be interpreted in the context of the phenotypic complexity and other challenges of rare disease research.

Genetically based therapies increase, decrease, or otherwise modify expression of a gene via DNA or RNA-based techniques, which can lead to both short- and long-term toxicities.4,5 Currently, all commercially available genetic therapies alter gene expression in some way, and affect only the proband receiving therapy and should be paired with appropriate genetic counseling as it relates to family planning and risk for future generational inheritance, as well as impact on carrier relatives if relevant. Genome editing, either somatic or germ-line, is currently present only in the research setting; as it targets the proband’s DNA permanently by removing or correcting a pathogenic variant, it may also affect the germline and subsequent generations. Several potential concerns remain regarding gene therapy: Cellular immunity as well as complement activation have been identified in tolerability concerns that have arisen in multiple programs.4 Individuals with preexisting immunity to the viral vector are also not candidates for gene therapy with current technology, except for neonates who can show clearance of passively transferred maternal antibodies over weeks; some investigators have begun to study plasmapheresis and other measures to attenuate this issue and it may also allow for repeat dosing if optimized. In the DMD programs, the microdystrophin protein expressed is not fully functional and thus disease expression over time is expected but hoped to be ameliorated compared with natural history; in any gene transfer, penetrance and efficacy may vary across tissues because of tropism and other factors.4 Durability is also a concern. As an example, in DMD, since the genome of adeno-associated viruses (AAWs) generally does not integrate into the host genome, the micro/ minidystrophin transgene would persist in host cells as episome and would not be replicated during mitosis. Thus, in any tissue with cell division or turnover, the transgene may eventually become diluted or lost—although satellite cells may harbor some reserve. Alternatively, some have raised the possibility of the rare occurrence of AAV vector integration; if this happens at any significant frequency, it raises the concern of altering the expression of endogenous genes and potential issues such as oncogenicity over the life span.6
With early diagnosis and intervention, hope is beginning to emerge for a subset of those with neurodegenerative genetic disorders to remain asymptomatic with treatment. Examples in nature occurred prior to having targeted treatments, such as families where a pediatric diagnosis of SMA led to testing of relatives and individuals with genetic SMA along with high SMN2 copy number received a diagnosis late in life and were asymptomatic. The standard of care for most inherited neurologic disorders includes interdisciplinary screening and management of neurologic and other systemic comorbidities; maximizing function and minimizing symptoms is the goal. It is important to reinforce with patients and their caregivers that this follow-up will continue to be required after receiving novel therapeutics. Currently available reviews and care consensus/care considerations guidelines often mention potential treatments on the horizon, but no guidelines that include targeted treatments are available to this point in 2022. The balance between target tissue expression—including the impact and durability of the protein expression achieved vs toxicity considerations with the medications themselves and potential off-target genetic and/or protein overexpression toxicities—requires extensive further research and long-term, real-world follow-up of those receiving treatment.

Continuing to engage with a specialized care team throughout life is therefore important both for monitoring for potential disease manifestations in tissues not optimally rescued via targeted therapy, and for monitoring regarding short- and long-term adverse effects of the interventions.

In the neuromuscular field, gene transfer is actively being investigated in research trials or on the near horizon for genetic amyotrophic lateral sclerosis, limb-girdle muscular dystrophies, glycogen storage disease type II (Pompe disease), giant axonal and Charcot-Marie-Tooth inherited neuropathies, and congenital myopathies and myasthenic syndromes. 2021 also heralded the sobering announcement of multiple deaths at higher vector doses in a gene transfer trial for myotubular myopathy, and the rare incidence of thrombotic microangiopathy after SMN gene transfer. Combination therapy with multiple genetically targeted treatments is occurring in SMA; both research trial and real-world data will be critical for evaluating the efficacy and tolerability of combination treatment, informing the ethical and economic considerations of access to these high-cost treatments across the spectrum of SMA severity. Targeting the phenotype is also continuing in active study for many disorders, such as myostatin inhibition in SMA for those already on genetically targeted therapies. It is likely that eventually a cocktail approach will be tailored with optimized timing of intervention to the individual, based on genotype and age of diagnosis as well as symptom burden; this would ideally be informed by disease biomarkers. The important question of whether there is an end point where risk outweighs benefit in those whose disease has progressed also requires further investigation.

The quest for treatment optimization in genetic neurodegenerative disorders will not be complete until an affected patient has no detectable signs or symptoms of disease because of successful early identification and customized treatment with minimal adverse effects. Those affected will likely continue to require long-term follow-up by specialized interdisciplinary teams for both optimization of health and long-term monitoring of potential complications of targeted treatments. We have entered the age of genetically targeted therapies in the neuromuscular clinic; there are many unresolved clinical, economic, and ethical questions that require extensive further research.
NeurologyLive® Remembers MJH Life Sciences®
Founder Michael J. Hennessy Sr

IT IS WITH HEAVY HEARTS that NeurologyLive® announces the great loss of Michael J. Hennessy Sr, 61, founder of MJH Life Sciences®, our publisher and parent company.

Hennessy’s passion for medical communications has made MJH Life Sciences® what it is today: a continually growing and successful organization committed to providing health care and related professionals and industries with the highest-quality information to ultimately improve care. Those who knew him in any capacity know he was a man of vision and purpose, and those traits have directly contributed to not only the longevity of the company that is his namesake, but also growth within it from the top down. It is difficult to say that anyone who encountered him was not changed for the better because of it.

Even with decades of success in professional ventures, Hennessy’s greatest accomplishment was that of his family. A father of 4 and a grandfather to 10, Hennessy’s role as the patriarch of the Hennessy family extended beyond his relatives. His passion and drive served as an inspiration for the many associates who have built upon the foundations he laid.

Hennessy’s passion for building successful ventures and businesses began after he graduated from Rider University in 1982, when he pursued a career in medical publishing. Going from a sales trainee to an eventual chief operating officer of Medical World Business Press, his early success was merely a glimpse into what was ahead. In 1993, Hennessy launched Multimedia Healthcare, LLC, building a portfolio of award-winning clinical journals. These endeavors led him to a new approach to print and digital publishing with Intellisphere (now part of MJH Life Sciences®).

Over the years—and inspired by his wife, Patrice “Patti” Hennessy, and her 2011 ovarian cancer diagnosis—Hennessy was dedicated to improving the lives of patients, focusing on cancer and rooting it deeply into the halls of MJH Life Sciences®. As a complement to the industry-leading OncLive® platform, he developed the Giants of Cancer Care® awards to recognize the leaders and pioneers who often go unrecognized for their contributions to advancing oncology care, and he further strengthened his commitment to education by acquiring CURE Media Group in 2014, among others. Today, that goal of improving patient care has expanded into every medical specialty, including the very focus of our publication: neurology.

Hennessy’s legacy and “family first” mantra will live on through his family and MJH Life Sciences®. The NeurologyLive® and MJH Life Sciences® family mourns the loss of a man with true entrepreneurial spirit and an unmatched passion and desire to advance the field of health care. Through his legacy, we will continue to collaborate, educate, and inspire hope to many of the future.

Michael J. Hennessy, 61, the son of John J. Hennessy and Vincent Ann (Lamenza) Hennessy, was born in New Brunswick, New Jersey, and resided in Marco Island, Florida. He died on Sunday, November 21, 2021, in Marco Island. Hennessy was preceded in death by his college sweetheart and beloved wife of 36 years, Patrice Lynn Hennessy of Millstone, New Jersey.

Hennessy is survived by his children and their spouses, Shannon Hennessy Pulaski and her husband, Matthew; Ashley Hennessy Talamo and her husband, Philip; Michael Hennessy Jr and his wife, Rachel; and Christopher Hennessy Sr and his wife, Jordan. He is also survived by the loves of his life, his grandchildren: Brooke, Riley, Luke, Philip, Hailey, Harper, MJ, Maggie, Christopher Jr, and Eric.
THE POTENTIAL ROLE OF EPSTEIN-BARR VIRUS IN MULTIPLE SCLEROSIS

Learn about the associations between Epstein-Barr virus and Multiple Sclerosis as well as the potential role of Epstein-Barr virus in Multiple Sclerosis pathogenesis.

In this iPub®, the experts will:

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<td>Educate on data supporting key associations between Epstein-Barr virus and multiple sclerosis.</td>
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<td>Describe how Epstein-Barr virus may help drive pathogenic mechanisms underlying progressive multiple sclerosis.</td>
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Dr. Lawrence Steinman
Zimmermann Professor of Neurology & Neurological Sciences, Pediatrics Beckman Center for Molecular Medicine Stanford University

Dr. Mark Freedman
Professor of Medicine – Neurology, University of Ottawa

ON-DEMAND BROADCAST

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**Focused Ultrasound Device Is Approved for Advanced Parkinson Disease**

By Abby Reinhard

The Exablate Neuro device has received FDA approval to treat patients with advanced Parkinson disease experiencing mobility, rigidity, or dyskinesia symptoms, Insightec announced in November 2021.¹ The device uses focused ultrasound waves to target the globus pallidus without requiring an incision. The device requires no brain implants and poses a lower risk of infection compared with invasive surgery. It has already been approved for treatment of medication-refractory essential tremor (ET), granted in 2016, and was later approved for the treatment of tremor-dominant PD in 2018. A total of 37 centers in the US are currently using the device to treat this patient population.

Using a helmet-shaped ultrasound inducer, the Exablate Neuro device also has adjustable advanced focusing algorithms to ensure beams converge at the desired target on the patient’s skull. The process is performed on an outpatient basis in an MRI suite, with treatment guided by the MR imaging. “Movement disorder neurologists now can offer their patients with Parkinson a less invasive surgical option as part of their treatment plan,” Paul S. Fishman, MD, PhD, professor of neurology, pharmacology, and neurobiology at the University of Maryland School of Medicine, said in a statement.¹

The 2018 FDA approval for treatment of patients with tremor-dominant PD was based on data from a randomized clinical trial (NCT01772693) examining the safety and efficacy of focused ultrasound (FUS) thalamotomy in managing medically refractory, tremor-dominant PD, also measuring the magnitude of placebo response. Twenty-seven patients with tremor-dominant PD were included in the pilot trial, randomized 2:1 to undergo FUS thalamotomy (n = 20) or a sham procedure (n = 7). Results showed a statistically significant difference in on-medication Clinical Rating Scale for Tremor A+B treated hand tremor subscores, with those in the FUS thalamotomy group improving by a median of 7 points or 62% (IQR, 22%-79%) from a baseline of 17 points (IQR, 10.5-27.5), and those in the sham group improving by 2 points or 22% (IQR, –11% to 29%) from a baseline of 23 points (IQR, 14.0-27.0). Similarly, on-medication median Unified Parkinson’s Disease Rating Scale Motor scores improved by 8 points (IQR, 0.5-11.0) from a baseline of 23 points (IQR, 15.5-34.0) following FUS thalamotomy and 1 point (IQR, –5.0 to 9.0) from a baseline of 25 points (IQR, 15.0-33) after sham procedures.²

The initial FDA approval, granted in 2016, made Exablate Neuro the first FUS device to receive approval for treatment of medication-refractory ET with noninvasive MR-guided FUS thalamotomy. Treatment with transcranial FUS is performed while patients are awake and responsive, delivering incremental increases in energy until a reduction of tremor is achieved.³

**Efgartigimod Receives Green Light for Generalized Myasthenia Gravis**

By Matt Hoffman

The FDA has approved efgartigimod, Argenx's first-in-class investigational antibody fragment to target the neonatal Fc receptor, for the treatment of generalized myasthenia gravis (gMG) in adults who test positive for the anti-acetylcholine receptor (AChR) antibody, according to an announcement in December 2021.³

The drug will now be marketed as Vyvgart. The agency had previously granted the therapy both fast track and orphan drug designations.

The biologics license application submitted to the agency was supported by data from the phase 3 ADAPT trial (NCT03669588).² Of the 167 patients randomized to an evaluation arm in the ADAPT trial, 84 were randomized to the efgartigimod group and 83 to the placebo group. Of the full population, 77% (n = 129) were acetylcholine receptor–antibody positive (AChR-Ab+).

The findings of that study suggest that efgartigimod was well tolerated and efficacious in treating patients with gMG, with the drug meeting the primary end point by improving gMG activities of daily living (MG-ADL) scores for patients with AChR-Ab+ gMG compared with those in the placebo group (67.7% vs 29.7%; P < .0001). Additionally, 40.0% of efgartigimod-treated AChR-Ab+ patients achieved minimal or no symptoms, compared with 11.1% of those treated with placebo.³

A list of secondary end points that demonstrated significant differences in the efgartigimod arm for AChR-Ab+ patients compared with placebo include MG-ADL responders in the overall population, as well as both AChR-Ab+ and AChR– patients (P < .0001), and time on trial in clinically meaningful improvement, defined as an MG-ADL improvement of 2 points or greater (P < .0001). Additional significant differences from the efgartigimod group for AChR-Ab+ patients compared with placebo were fast onset of response on MG-ADL score, defined as onset observed in first 2 weeks (P < .0004).³⁴

A sustained response was observed in 88.6% of AChR-Ab+ patients who met the primary end point for at least 6 weeks, 56.8% for at least 8 weeks, and 34.1% for at least 12 weeks. Furthermore, 70.6% of AChR-Ab+ patients received a second treatment cycle, compared with 25.6% of placebo patients.³⁴

Of those in the treatment group 77% (n = 65) experienced treatment-emergent adverse events (TEAEs), whereas 84% (n = 70) of the placebo group did. The most frequent TEAEs reported were headache (efgartigimod, 29% [n = 24]; placebo, 28% [n = 23]) and nasopharyngitis (efgartigimod, 12% [n = 10]; placebo, 18% [n = 15]). Five percent (n = 4) of efgartigimod-treated patients and 8% (n = 7) of patients in the placebo group had serious TEAEs, and 3 patients (4%) in each group discontinued treatment during the study.³

An open-label extension trial of the therapy, called ADAPT+ (NCT03770403), is ongoing, and there are plans to explore a potential subcutaneous administration of the agent in addition to its current intravenous infusion formulation.

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

JOURNAL ROUNDUP

SAGE Test Detects Early Dementia 6 Months Sooner Than MMSE
By Abby Reinhard

The Self-Administered Gerocognitive Examination (SAGE) test was evaluated in a recent longitudinal study, with investigators concluding the assessment identified mild cognitive impairment (MCI) conversion to dementia at least 6 months ahead of the nonself-administered Mini-Mental State Examination (MMSE) in 5 diagnostic subgroups.1

The study included a total of 424 patients, 40 of whom had subjective cognitive decline (SCD), 94 of whom were MCI nonconverters to dementia, 70 of whom were MCI converters to dementia, and 220 of whom had Alzheimer disease (AD) dementia. Of the MCI converters to dementia, 49 converted to AD dementia and 21 progressed to non-AD dementia.

The SAGE test showed a statistically significant decline from baseline scores at least 6 months ahead of the MMSE for patients who converted from MCI to AD dementia (14.4 vs 20.4 months), patients who converted from MCI to non-AD dementia (14.4 vs 32.9 months), and patients with AD dementia (8.3 vs 14.4 months). When looking at annual SAGE and MMSE scores, MCI converters to dementia declined at rates of 1.91 points per year (P < .0001) and 1.68 points per year (P < .0001), respectively. For those with AD dementia, SAGE and MMSE scores declined at rates of 1.82 points per year (P < .0001) and 2.38 points per year (P < .0001), respectively. Scores were stable for patients with SCD who were MCI nonconverters. The patients who were identified as being likely to eventually develop dementia had a 2- to 3-point decline in SAGE scores 12 to 18 months from baseline, a significant decline.

Annual rates of change were originally performed on 665 consecutive patients from The Ohio State University Memory Disorders Clinic, and patients with at least 3 visits 6 months apart were evaluated with both assessments. The SAGE test is a pen-and-paper assessment that takes approximately 5 minutes to complete.2

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

Similar Outcomes Are Observed With Asleep and Awake DBS for Parkinson Disease
By Marco Meglio

Findings from the single-center, prospective GALAXY clinical trial (NTR5809) showed no between-group difference in cognitive, mood, and behavioral adverse events, as well as equal improvement in motor function, in patients with Parkinson disease (PD) who underwent deep brain stimulation (DBS) of the subthalamic nucleus with either general (asleep) anesthetic or local (awake) anesthetic.1

Senior author Rick Shuurman, MD, PhD, professor of neuroscience at Amsterdam University Medical Centers, and colleagues, collected data on 110 patients with advanced PD and motor response fluctuations who were randomized 1:1 to awake (n = 56) or to asleep (n = 54) DBS surgery, with the primary outcome follow-up visit conducted 6 months after the procedure. The primary outcome was a composite score of cognitive, mood, and behavioral adverse events that was composed of findings in 4 areas.

Primary outcome data were available for 103 patients at the conclusion of the 6-month period. At this time, no differences in the primary outcome were observed between the general and local anesthesia groups. A composite score of 1 or more occurred in 15 of 52 patients (29%) in the local anesthesia group and in 11 of 51 patients (22%) in the general anesthesia group (odds ratio [OR], 0.7; 95% CI, 0.3-1.7). These results did not change in a multivariable regression model (adjusted OR, 0.7; 95% CI, 0.3-1.7).

Shuurman et al also looked at secondary outcomes that included change in the Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS), the patient assessment of surgical burden, and operative time. Six months after surgery, the mean improvement in motor symptoms, reflected by change in MDS-UPDRS during the off-medication phase, was not different between the groups. Investigators recorded changes of −27.3 points (SD, 17.5; 52% improvement) in the local anesthesia group, compared with −25.3 points (SD, 14.3; 50% improvement) in the general anesthesia group (mean difference, −2.0 points; 95% CI, −8.1 to 4.2).

Neither group demonstrated an advantage in improvement of subscores of tremor, rigidity, bradykinesia, and gait and balance. The results observed in MDS-UPDRS scores remained did not change in the multivariable regression analysis (β = 1.1; 95% CI, −3.7 to 5.9).

Results using a 7-point Likert-type scale, with higher scores representing greater satisfaction, showed that asleep surgery was experienced as less burdensome by patients. The median experienced burden of surgery was 5.0 (IQR, 2.0-7.0) in the local anesthesia group, compared with 1.0 (IQR, 1.0-2.5) in the general anesthesia group (P < .001).

Furthermore, the median satisfaction about the outcome of DBS after 6 months was 6.5 (IQR, 6.0-7.0) in the local anesthesia group, compared with 7.0 (IQR, 6.0-7.0; P = .23).

Patients in the local anesthesia group had a mean operative time of 323 (SD, 47) minutes compared with 297 (SD, 53) minutes in the general anesthesia group. There was no between-group difference in the number of microelectrode tracks used for the recordings (Mann-Whitney U = 1370.50 [Z = −.0775; P = .44]).

For a full list of references, see the article on NeurologyLive.com.
MIND MOMENTS™ SPOTLIGHT
Multimedia highlights from our coverage of neurologic disorders

#MindMoments with NeurologyLive

TOP TWEETS

AASM Membership | @AASMMembership
Take a look back at @neurology_live’s top video interviews of 2021, featuring #SleepMedicine experts and AASM members Lynn Marie Trotti, MD, MSc, and Anita Shelgikar, MD, MHP (AnitaVS).

EEGTalk | @EEGTalk
…before him, ICU #EEG was chaos…. Are you ready? @ACNS_org @CliniNeurophys @Yale @fabnascimen @curedravet @yesILAE @neurology_live

Ctrl M Health | @ctrmhealth
“Trigger avoidance is usually ineffective for #migraine and sometimes even detrimental to patients.” Learn why & how to redirect patients to more effective strategies in our latest for @neurology_live by Dr Michael Marmura @JeffHeadacheCtr #MedTwitter

Parkinson & Movement Disorder Alliance | @PMDAlliance
We’re excited to collaborate, build community, and positively impact physicians & patients through @neurology_live’s empowering platform.

Imad Najm | @imadmnajm
Exciting work in imaging, genetics, and AI with major impacts on #epilepsy management! Thank you @neurology_live @CleClinicMD @Hantus @AMoosaMD @LalDennis @irenezhongwang @CleClinicNeuro.

EVALUATING 3K3A-APC IN PATIENTS WITH ALS: KENT PRYOR, PHD
Kent Pryor, PhD, chief executive officer of ZZ Biotech, outlines the design of the phase 2 trial of 3KA-APC (NCT05039268), which will enroll 16 patients with amyotrophic lateral sclerosis, divided into 2 cohorts to receive 5 doses of either 15-mg or 30-mg 3K3A-APC.

GUIDELINES NEEDED FOR TREATING HEADACHE IN EMERGENCY DEPARTMENTS: ANNE-MAREE KELLY, MD
Anne-Maree Kelly, MD, director of the Joseph Epstein Centre for Emergency Medicine Research, discusses why guidelines developed by international bodies would provide crucial direction for emergency departments in how they treat presenting headache.

THE SHORTAGE OF NEUROLOGISTS
Jennifer Majersik, MD, MS, chief of the Division of Vascular Neurology and professor of neurology at the University of Utah School of Medicine in Salt Lake City, who, along with 9 other colleagues, authored a report from the American Academy of Neurology 2019 Transforming Leaders Program on the ongoing shortage of physicians in neurology, offers her perspective on the challenge and how it can be addressed from an individual and institutional level.

TREATING PEDIATRIC MIGRAINE
Christina Szperka, MD, MSCE, assistant professor of neurology in pediatrics and director of the Pediatric Headache Program at Children’s Hospital of Philadelphia in Pennsylvania, offers her thoughts on the current state of clinical care and awareness of pediatric migraine and shares her insight into the changes the treatment landscape has undergone.

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Perampanel Is Effective, Well Tolerated in Lennox-Gastaut Syndrome

By Abby Reinhard

DATA FROM A RECENT STUDY suggest that treatment with perampanel (Fycompa; Eisai) is safe and well tolerated in patients with Lennox-Gastaut syndrome (LGS). The findings were presented at the 2021 American Epilepsy Society Annual Meeting.

Following the identification of 35 patients with LGS, investigators assessed a total of 33 for retention. Of those, they assessed 30 patients for effectiveness and 22 for safety and tolerability of treatment with perampanel for focal-onset and/or generalized-onset seizures. Of the 30 patients assessed for effectiveness at the time of the last visit, 17 (56.7%) responded to treatment, defined as a 50% or greater reduction in seizure frequency, and 1 (3.3%) reported seizure freedom, defined as no seizures since at least the prior visit. A total of 7 patients (23.3%) had unchanged seizure frequency and 2 (6.7%) experienced worsening seizure frequency.

"Treatment of LGS is challenging due to the presence of multiple seizure types and comorbidities," wrote study investigator Carlo Di Bonaventura, MD, of the Department of Human Neurosciences, Sapienza University of Rome, Italy, and colleagues.1 "In this difficult-to-treat, small population of patients with LGS, perampanel demonstrated effectiveness and was generally well tolerated when used in everyday clinical practice."

At baseline, the mean perampanel dose was 2.0 mg/day (SD, 0.0) and 6.1 mg/day (SD, 2.8) at the last visit. Investigators observed retention rates of 90.9% (30 of 33 patients) at 3 months, 75.8% (25 of 33 patients) at 6 months, and 63.3% (19 of 30 patients) at 12 months.

The mean amount of time spent undergoing treatment with perampanel was 10.3 months (95% CI, 8.2-12.0). Patients most often discontinued treatment due to adverse events (AEs; 16.7%), lack of efficacy (13.3%), or a combination of AEs and lack of efficacy (6.7%). Among the 22 patients assessed for safety and tolerability, 15 (68.2%) experienced AEs and 7 (33.3%) experienced psychiatric AEs. Five patients (22.7%) reported irritability, 2 (9.1%) reported instability or ataxia, and 2 (9.1%) reported somnolence.

Data from another recent study also suggest that perampanel significantly reduced epileptic seizures, migraine attacks, and the use of monthly rescue migraine medications over a 12-month period in a cohort of patients with comorbid epilepsy and migraine. In the observational study, senior author Claudio Liguori, MD, a neurologist at the Epilepsy Center, University of Rome Tor Vergata in Italy, and colleagues aimed to confirm the effectiveness of perampanel in 31 enrolled patients (mean age, 40.13 years; 67.7% women) with comorbid epilepsy and migraine.2 Fourteen patients (45.2%) started perampanel with 1 concomitant antiseizure medication (ASM), and 17 patients (54.8%) started the study drug in association with 2 ASMs.

Most patients (n = 27; 87.1%) retained treatment at 12 months, with 2 patients having discontinued treatment due to lack of efficacy and 2 due to AEs. Treatment with perampanel over the 12-month period resulted in seizure freedom for 11 patients. Seven patients experienced at least a 75% reduction in seizures.
CBTip Demonstrates Pronounced Results in Psychogenic Nonepileptic Seizures

By Marco Meglio

RESULTS FROM A RETROSPECTIVE STUDY showed significant improvements in seizure frequency, anxiety, and depression in patients with psychogenic nonepileptic seizures (PNES) when treated with cognitive behavioral therapy–informed psychotherapy (CBTip) for more than a 12-week period. These results were presented at the 2021 American Epilepsy Society Annual Meeting, by Becky Tilahun, PhD, a clinical psychologist at Cleveland Clinic, in Ohio.

The 2-part analysis included 160 patients who were treated with at least 7 sessions of CBTip for a 12-week period. The first analysis looked at change in outcomes in pretreatment and 90-day patient reported outcome (PRO) scores, whereas the second analysis looked at those in a flexible treatment schedule by comparing pretreatment scores with 90-day to 1-year post–initial visit scores.

“One of the good things about this type of intervention is that CBTip is specifically designed for patients with nonepileptic seizures,” Tilahun told NeurologyLive®. “We know that many patients with PNES or other similar symptoms are...not very adherent and tend to drop out of treatment early when it’s a more general CBT, whereas this specific type of intervention addresses seizure triggers [and] preseizure auras and is tailored to the type of symptoms and struggles that they have.”

Investigators recorded patient-reported assessments on depression, anxiety, and quality of life monthly prior to each visit using the Patient Health Questionnaire-9 (PHQ-9), General Anxiety Disorder-7 (GAD-7), and Quality of Life in Epilepsy-10 (QOLIE-10) questionnaires. Using single-predictor linear regression models, the investigators found no significant change in outcomes based on number of visits (7–11 or more).

After computing t-tests and Mann-Whitney U tests, the investigators observed no significant change in seizure frequency, with a posttreatment mean of 1.3 seizures (standard deviation [SD], 1.1) per day compared with 0.3 (SD, 0.1) at pretreatment. Additionally, CBTip showed no significant change in outcomes such as depression (pretreatment PHQ-9 scores, 12.2 [SD, 5.9]; post treatment, 11.3 [SD, 7.3]; P = .455), anxiety (pretreatment GAD-7 scores, 12.3 [SD, 5.3]; post treatment, 10.1 [SD, 6.4]; P = .149), and quality of life (pretreatment QOLIE-10 scores, 25.5 [SD, 9.2]; post treatment, 22.0 [SD, 8.5]; P = .90).

In the second analysis, Tilahun and colleagues identified a significant improvement in seizure frequency (pretreatment seizures per day, 0.5 [SD, 0.9]; post treatment, 0.2 [0.4]; P = .449), depression (pretreatment PHQ-9 score, 13.3 [SD, 6.5]; post treatment, 9.9 [SD, 7.5]), and anxiety symptoms (pretreatment GAD-7 score, 12.0 [SD, 5.8]; post treatment, 9.2 [SD, 6.2]). Only 10 patients had data from seizures per day in 6 months, and 5 (50%) improved by 50% or more in the number of seizures per day.

“Our suspicion is that even the patients in the 12-week sample may have shown some improvement if we [had] had a larger sample size. We were also wondering if the longer duration was more beneficial, [as] that’s where we saw the benefits, or if it’s just the sample size,” Tilahun said. “The conclusion that we drew is that we need more research to prove if that’s the case. Maybe longer, more intense care is needed, or [maybe it is] because patients came infrequently and didn’t come weekly. We are curious to see what are the specific factors that helped these patients improve.”

Looking forward, Tilahun noted that she wants to evaluate this type of approach in a virtual setting. “There’s a scarcity of providers for functional neurological disorders, so one of the ways you’re going to [treat] this is to try different approaches,” she said. “With more research, these interventions will be more approachable and accessible for patients as opposed to just saying, ‘Well, you don’t respond to one type of approach, [and] there is no other option for you.’”

REFERENCES


Ganaxolone Is Associated With Decreased Seizure Frequency in Patients With CDD, LGS

By Abby Reinhard

DATA FROM A POST HOC ANALYSIS of a recent study suggest that treatment with the positive allosteric GABA<sub>A</sub> receptor modulator ganaxolone (Marinus Pharmaceuticals) was associated with decreases in major motor seizure frequency (MMSF) in patients with CDKL5 deficiency disorder (CDD) and comorbid Lennox-Gastaut syndrome (LGS). The findings were presented at the 2021 American Epilepsy Society Annual Meeting.

A total of 7 patients in the phase 3 Marigold study (NCT03572933) had a codiagnosis of LGS. During the double-blind period, investigators randomized 2 to receive treatment with ganaxolone and 5 to receive placebo. Patients in this subgroup ranged in age from 3 to 19 years and experienced a median of 88.7 MMSs over 28-day increments. Patients were also being treated with a median of 3 concomitant antiseizure medications.

After 1 patient did not enter the 17-week open-label extension (OLE) period, a total of 6 patients from the subgroup were included in analyses from the OLE, with 4 continuing to receive ganaxolone and 2 receiving ganaxolone after previously receiving placebo. During the OLE, investigators, led by Ian Miller, MD, vice president of clinical development at Marinus Pharmaceuticals, observed percentage changes in MMSF of –25.4% and –43.5% in the 2 patients who had previously been treated with ganaxolone over the 17-week double-blind period.

Of those who received ganaxolone in the OLE after receiving placebo in the double-blind period, 2 patients demonstrated a percentage change of –21.0% and –36.3% in MMSF; whereas 2 patients showed no improvement in MMSF (4.6% and 27.1% change). Investigators noted that the treatment was well tolerated in the LGS subgroup, with no new safety findings identified.

“CDD is a developmental and epileptic encephalopathy with a complex phenotype, including drug-resistant epilepsy. CDD is a genetic diagnosis resulting from variants in the CDKL5 gene. LGS is a clinical diagnosis characterized by multiple seizure types, a slow spike-and-wave pattern on [electroencephalogram], and neurodevelopmental disability,” Miller et al wrote. “As a result, patients with CDD as an etiological diagnosis may also have a phenotypic diagnosis of LGS. Ganaxolone, an investigational neuroactive steroid, demonstrated a significant reduction in major motor seizures in a phase 3, placebo-controlled trial in CDD. A subgroup analysis in patients who also met diagnostic criteria for LGS was performed to gain preliminary insights on the effects of ganaxolone in LGS.”

Investigators randomized a total of 101 patients in the Marigold study, a double-blind, placebo-controlled trial of ganaxolone in patients with a pathogenic CDKL5 mutation and 16 or more major seizures each month. MMS types included bilateral tonic, generalized tonic-clonic, atonic/drop, bilateral clonic, and focal to bilateral tonic-clonic.

Patients with comorbid LGS were located via medical history and were aged between 2 and 19 years. Participants in Marigold underwent a 6-week baseline period and a 17-week double-blind treatment period. The 17-week OLE was also open to those who completed the double-blind period.

REFERENCE

VNS Implantation, Dietary Therapies Reduce Seizures in Children With TSC, DRE

By Abby Reinhard

DATA FROM A RETROSPECTIVE CHART review suggest that dietary therapies and vagus nerve stimulation (VNS) were effective in reducing seizures in children with tuberous sclerosis complex (TSC) and drug-refractory epilepsy (DRE) who were ineligible for epilepsy surgery.

Investigators, including Robyn Whitney, MD, assistant professor of pediatrics at McMaster Children’s Hospital, McMaster University, in Ontario, Canada, assessed seizure outcomes and adverse effects (AEs) in 20 children. Twenty patients (75%) were treated with dietary therapies, including the classic ketogenic diet (n = 10), the medium chain triglyceride diet (n = 4), and the modified Atkins diet (n = 1). Patients had a median age of 4.2 years (IQR, 2.5-11.7) at initiation, and 10 of 15 had persistently good ketone levels.

According to data presented at the 2021 American Epilepsy Society Annual Meeting, after a median follow-up duration of 23 months, 7 children (47%) had a greater than 50% reduction in seizure frequency when treated with dietary therapy. Following a median of 17 months (range, 1-108), 11 participants
discontinued the diet: 3 due to AEs, 3 due to ineffectiveness, 2 due to improved seizure control, and 3 due to other reasons. The most common AEs related to diet were constipation, in 7 participants (47%), and vomiting, in 5 participants (33%).

Children who underwent VNS had a median age at implantation of 12 years, and 5 of the 9 who began VNS were referred to the treatment following failure or discontinuation of dietary therapy. VNS therapy was well tolerated, and 6 of 9 patients treated had a 50% or greater reduction in seizures after a median follow-up period of 37 months. Seven of 9 patients had a response to the magnet, with 4 reporting aborted seizures, 2 reporting reduced seizure duration, and 1 reporting reduced seizure severity.

Patients had a median age at seizure onset of 5 months (range, 2 days to 2.5 years), and all had daily seizures when beginning dietary therapy or at the time of VNS implantation. The most common seizure type was focal seizures, and investigators observed TSC2 variants in 11 of 15 patients (73%).

The retrospective review included children who were treated with dietary therapy or VNS therapy at 2 academic centers in Ontario, Canada, between 2010 and 2020. Investigators noted the small number of studies investigating the effectiveness of dietary therapies and VNS in treating TSC, and the resultant need for a systematic review and meta-analysis of the existing data to determine the effect.

Robyn Blackford, RD, LDN, a registered dietician at Ann & Robert H. Lurie Children’s Hospital of Chicago, in Illinois, recently spoke with NeurologyLive® on the importance of understanding different dietary approaches to help control seizures, specifically the ketogenic diet.

“From a surgical aspect, it works on these folks. I’d go out on a limb and say that within the distant future, it will be almost mandatory that you try cenobamate as one of those drugs before seizure surgery,” Rosenfeld said. “Obviously, that will be up for opinion and debate, but I think that with the efficacy numbers we’ve seen between that 20% to 35% seizure rate, that’s quite good news.”

Of the 177 patients still receiving cenobamate, 65 had prior epilepsy-related surgery, with a mean duration of 23.5 months at data cutoff. At this time point, 29.2% (19 of 65) had SF for at least 12 months. For nonsurgical patients (n = 155), 26.5% (n = 41), 27.1% (n = 42), and 39.4% (n = 61) achieved SF for at least 12 months at data cutoff, last clinic visit, and any consecutive interval, respectively.

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CONFEREE HIGHLIGHTS

Cenobamate Offers Unique Benefit for Surgically Refractory Epilepsy

By Marco Meglio

FINDINGS FROM A POST HOC analysis, presented at the 2021 American Epilepsy Society Annual Meeting, showed that cenobamate (Xcopri; SK Life Science), provided additional seizure freedom (SF) benefit for patients with uncontrolled focal seizures taking 1 to 3 antiseizure medications (ASMs) who were refractory to a prior epilepsy-related surgery. The data were from the long-term, phase 3, open-label safety study YKP3089C021(NCT02535091), which included 1345 patients aged 18 to 70 years. In this analysis, senior author William E. Rosenfeld, MD, and colleagues recorded the percentage of patients achieving SF for at least 12 months up to last clinic visit and those who achieved SF after 12 months at any interval, not just at last visit.

The trial began in July 2016 and had a total duration of up to 43 months at data cutoff on September 1, 2019. Focal seizure data were available for 240 patients, of whom 177 were still receiving the study drug as of data cutoff. The mean duration of time on study for those patients was 33.6 months. Eighty-five (35.4%) of the available cohort had prior epilepsy-related surgery. In this group, 20 (23.5%) had achieved SF for at least 12 months since the last clinic visit and 24 (30.6%) had SF for at least 12 months during any interval.

Rosenfeld, a neurologist at The Comprehensive Epilepsy Care Center for Children and Adults in St Louis, Missouri, noted that these results should give clinicians the confidence to prescribe cenobamate more often for this patient population. “We’ve come very far with our seizure surgery, and it’s become safer and safer, but there are still risks whenever you perform a surgery. If you can give a medicine and control the patient in that way, that’s fantastic and avoids the potential risks of surgery,” he told NeurologyLive®.

The cohort included 31 patients who had been treated with only vagus nerve stimulation (VNS) or responsive neurostimulation (RNS); 40 patients who had at least 1 procedure that was not VNS or RNS; and 14 patients who had both VNS and a resection, ablation, or disconnection surgery. Across all surgical procedures, the percentage of those receiving cenobamate who had SF for at least 12 months ranged between 20% and 35.7%.

“From a surgical aspect, it works on these folks. I’d go out on a limb and say that within the distant future, it will be almost mandatory that you try cenobamate as one of those drugs before seizure surgery,” Rosenfeld said. “Obviously, that will be up for opinion and debate, but I think that with the efficacy numbers we’ve seen between that 20% to 35% seizure rate, that’s quite good news.”

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Since the FDA approved cenobamate in 2019 to treat partial-onset seizures, an abundance of data have further bolstered the drug’s safety and efficacy profile, including 2 post hoc analyses from the trial published in October 2021. These data showed that long-term treatment with cenobamate, lasting up to 40.2 months, provided safe and effective reduction of seizure frequency and was associated with concomitant ASM dose reductions.²

SK Life Science presented a total of 6 abstracts at AES 2021, including data on the effects of cenobamate by focal seizure subtypes, those with uncontrolled focal seizures in routine clinical practice, and durability of seizure control with adjunctive cenobamate. They also presented a meta-analysis or indirect comparison of cenobamate to other ASMs for the treatment of uncontrolled focal seizures and data on patients’ plasma concentrations after reaching at least 50% or 100% responder rates over a period of 1 year.³

REFERENCE


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Potential of Neuropalliative Care Is Evaluated for Patients With Drug-Resistant Epilepsy

By Abby Reinhard

RESULTS FROM A RECENT needs evaluation of neuropalliative care (NPC) for patients with drug-resistant epilepsy found that although most patients were not aware of NPC, they had a positive response upon learning more about NPC goals. Data presented at the 2021 American Epilepsy Society Annual Meeting, showed that investigators identified different NPC services for this patient population to assist in coping with life with seizures.¹ A total of 20 adults with drug-resistant epilepsy and a mean age of 39 years (range, 27-61; SD, 9.4) volunteered to complete a 2-hour interview about their identity, perceptions, experiences, and needs in terms of living with the condition.

Patients were read a description of NPC and asked if they thought it had potential to play a role in their care. They also completed the Quality of Life in Epilepsy-10 (QOLIE-10) questionnaire, which is typically used in epilepsy clinics, and the McGill Quality of Life Questionnaire (MQOL), which is generally used in NPC clinics. Although full analyses of the interviews and surveys are ongoing, investigators led by Alison Hixon, MD, PhD, a neurology specialist in the neurology department at Barnes-Jewish Hospital in St Louis, Missouri, found that identity and relationships were altered following epilepsy diagnosis for 5 interviewees. Four patients’ responses revealed difficulties with coping, indicating issues that could be addressed by NPC, namely a lack of planning for the future, a need for social and spiritual support, and communication gaps with epilepsy providers. Four participants in total had heard of NPC and only 2 could provide descriptions, both of which were focused on aging and dying. Three participants expressed an interest in NPC, 1 was unsure about the benefit, and 1 was not interested.

"It is estimated that up to 70% of individuals can control seizures with optimal medical management, yet seizure freedom is not a reality for millions of epilepsy sufferers despite surgical options," Hixon et al wrote. “These [individuals with drug-resistant epilepsy] must continue to live with seizures that have large effects on daily life, including disruption from seizing, injuries from falls, medication [adverse] effects, interference with education and jobs, and mental health issues. One possible way to better support [those with drug-resistant epilepsy] is including NPC, a branch of palliative medicine focused on improving QOL in many other chronic neurological diseases through symptom management, psychosocial and spiritual support, and future planning.”

Despite their different time scales of 4 weeks vs 2 days, analyses of the QOLIE-10 and the MQOL for 19 patients (1 was lost to follow-up) suggested a strong correlation between the 2 questionnaires (R² = 0.68). Analyses are ongoing, but a high rate of existential distress on the MQOL questionnaire was reported by half of respondents when queried about life progress and self-worth.

Patients had a mean epilepsy duration of 16 years (range, 3-42; SD, 11.1) and experienced comorbidities, including depression (n = 14; 70%), anxiety (n = 12; 60%), and memory problems (n = 18; 90%). Patients had tried a mean of 5.9 antiseizure medications (range, 2-14; SD, 2.8).

REFERENCE

The “Grave Threat” Posed by the Shortage of Neurologists

With the physician deficit projected to grow larger within a decade, this global challenge has become a major focus of large organizations and medical societies.

By Kenneth Bender, PharmD, MA

A SHORTAGE OF NEUROLOGISTS IN the US is characterized as a “grave threat” to providing high-quality patient care and to the specialty of neurology in a recently published report from the American Academy of Neurology (AAN). 1

The gap between demand for and supply of neurologic services is widening due to several factors, including an aging population increasingly afflicted with neurodegenerative disorders, a volume of referrals that do not warrant neurologist intervention, and in some regions, neurologists choosing to practice subspecialties that are not among those most urgently required.

The report, titled A Shortage of Neurologists—We Must Act Now, was compiled by Jennifer Majersik, MD, MS, chief of the Division of Vascular Neurology and a professor of neurology at the University of Utah School of Medicine in Salt Lake City, and colleagues from AAN’s 2019 Transforming Leaders Program and points to numerous indicators of the shortage, with prolonged patient wait times among the most apparent.

“Pediatric neurology is among the top 3 pediatric subspecialties with the longest wait times, with 30% of clinics reporting new patient wait times of longer than 16 weeks,” Majersik and colleagues noted in the report. “Precise current data in adult neurology are not available, but reports agree that wait times are excessive, reported in 2012 as already at 35 days and rising, and with even longer delays in some markets.”

The disparity between the availability of neurologists and patients in need of treatment is not limited to the US, as described in an article in the Lancet Neurology in 2018. 2 In response to regional differences and their needs for neurologists, the Australian and New Zealand Association of Neurologists, for example, has constituted committees to address regional workforce disparities and task forces to recruit to particular patient care needs, such as for additional cognitive specialist neurologists and for subspecialists trained in endovascular clot retrieval in acute stroke.

Considering regional imbalances in Europe, Günther Deuschl, MD, president of the European Academy of Neurology from 2014 to 2018 and a professor of neurology at Christian-Albrechts University of Kiel in Germany, noted that in addition to neurologists often choosing urban over rural settings, there is also a westward “brain drain” from countries that are considered “less attractive” for physicians. “The only way to stop this is for countries that are losing neurologists to pay them more,” Deuschl told the Lancet Neurology.

But addressing such a complex challenge is more complicated than pay scale alone. Majersik told NeurologyLive® that identifying the best strategies to reverse the trend has been difficult because available data on the topic are not only limited but poor in quality.

“We tried to find where there were data in other diseases or other fields or early data that would be useful,” she said. “It makes it hard to settle on something when you don’t really know what’s going to be most effective. And that was our final recommendation: that we need research into these things so we can have a better idea of what will work.”

The working group did reach a consensus after several months through a series of phone calls, in-person meetings, Zoom calls, and emails. “We also had subgroups and then would meet back with the large group. So it was actually a pretty intense process,” she said.

Majersik and colleagues developed a 3-part plan to address the US shortage of neurologists, each part with several strategic components:

- “Shaping” demand for neurology services
- Enhancing the neurology workforce
- Valuing neurologists

JENNIFER MAJERSIK, MD, MS

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Shaping Demand at the Referral Base
In addition to recommending increased adoption of technologies such as telehealth and e-consults to increase capacity to respond to the demand for care, Majersik and colleagues propose a strategy of shaping that demand, principally through educating the referral base. They point out that many referrals to neurology do not warrant neurologist intervention, such as an incidental finding of minimal white matter changes on a brain MRI with a low likelihood of multiple sclerosis.

Taylor Harrison, MD, associate professor and assistant clerkship director in the Department of Neurology at Emory University School of Medicine in Atlanta, Georgia, concurs, attributing the quantity of referrals that may be unnecessary or inappropriate to the lack of adequate education and experiences in neurologic topics across other specialties and practitioners.

“I think one thing that complicates that whole situation is that in many specialties that come across neurological conditions, like family practice, internal medicine, orthopedics, emergency medicine—what have you—many times their residency program does not offer them an educational experience in neurology that helps kind of cement or build their foundation of knowledge in that area,” Harrison told NeurologyLive®. “This has been compounded by the large increase in midlevel providers who are practicing in various specialties and may have minimal to no foundational knowledge of neurological disorders, which ultimately results in more referrals to our [neurology] outpatient clinics.”

Majersik and colleagues support a recommendation from a previous AAN work group for a minimum 4-week clinical clerkship in the first 12 months of medical student clinical training directed at the recognition and management of neurologic diseases that a primary care practitioner is most likely to encounter. Such training, they suggest, should mitigate the “neurophobia” that is said to occur among both trainees and experienced practitioners, which they wrote “can lead to both under- and over-referring of patients to neurologists.”

Harrison described how Emory University School of Medicine has incorporated discussion of clinical conditions and neuroanatomical function into early neuroscience curriculum to heighten interest in the details of neuronal structure, transmitters, and pathways.

“Historically, we’ve learned about brain function through the examination of dysfunction,” Harrison observed. “It’s said we’ve learned about the brain, stroke by stroke, seeing how different strokes affect different areas of the brain and observing different deficits in the patient.”

Education to Enhance the Neurology Workforce
Majersik also considered the elements that can attract talented physicians to neurology in a conversation with NeurologyLive®. “Physicians want to work in areas that they can make a difference, and there are so many more therapies now. It’s an exciting time to go into the field. But there will also be more need to see all those patients,” she said.

Speaking at the American Neurological Association’s virtual annual meeting in October 2021 on a panel sponsored by the Association for University Professors of Neurology, S. Andrew Josephson, MD, professor and chair of the Department of Neurology at the University of California, San Francisco, described how the early neuroscience curricula can also heighten interest in practicing in neurology. He cautioned, however, that preresidency curricula should be broad, pointing out that students at that level are not yet thinking of pursuing neurology subspecialties.

“We’re not trying to get them to be vascular neurologists or tell them about what it’s like to be a neuroimmunologist,” Josephson noted in the session. “Rather, we’re trying to figure out how to get great people to become neurologists. What I do is educate them as to the benefits of our specialty with frank discussions, and we’ll talk about dispelling multiple myths. And then, hopefully, they make some great decisions, and we get more wonderful people to be neurologists.”

Josephson described findings from a 2019 medical graduate questionnaire that ranks the influence of various factors on the choice of specialty, noting the highest ranked was likelihood of personality fit, followed closely by specialty content, role model influence, and work-life balance. He noted that education cost/debt was the lowest-ranked factor and that less than half of those surveyed ranked income expectation as a strong influence.

Cathy Sila, MD, chair of the Department of Neurology at University Hospitals Cleveland Medical Center in Ohio, followed with a presentation on the noncommitted neurology resident and the challenge of better matching care requirements of an aging population with the supply of neurology subspecialists.

“Obviously, there’s a significant proportion of stroke, epilepsy, clinical neurophysiology, neuro critical care, and movement disorder specialists. But this doesn’t quite match with the demand ranking,” Sila told attendees. “The No. 1 demand is for general neurologists, with over 200 active ads for recruitment. No. 2 is a mix of stroke and hospitalists, reflecting inpatients needs for community hospitals and academic medical centers.

“Specialties such as epilepsy, neurophysiology, neurocritical care, and interventional therapies are really in a saturated market, where there’s an excessive number of trainees and it is not the demand.”

Sila offered several strategies for highlighting the areas of need to uncommitted residents, beginning with fostering a desire to serve the targeted community. She proposed developing a specific curriculum to promote the awareness of and skills for addressing the specific needs of the neurologic community.

The curriculum and training should build skill sets that include “cultural humility, cultural competence, understanding their unconscious biases in medical decision-making, [and] being aware of social determinants of health and those health disparities for neurologic conditions and the impacts of language, race, ethnicity, socioeconomic status, religion, sexual orientation, and gender identity,” Sila noted.

For examples of how these considerations can be built into programs, Rebecca Fasano, MD, associate professor of neurology in the Epilepsy Section and director of the Neurology Residency Program at the University of California, San Francisco, described how the early neuroscience curricula can also heighten interest in practicing in neurology. He cautioned, however, that preresidency curricula should be broad, pointing out that students at that level are not yet thinking of pursuing neurology subspecialties.

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—TAYLOR HARRISON, MD

Program at Emory University School of Medicine, told NeurologyLive® that they have recognized that medical students often choose their specialty based on which group of residents they feel they fit in with.

“Our residency program has a specific focus of supporting and increasing diversity in neurology. Forty percent of our residents are underrepresented minorities,” Fasano said.

“Our hope is that by working alongside neurology residents who look like them, more underrepresented minority students will choose this field.”

Fasano also recognizes the increased use of advanced practice providers (APPs) in neurology practices and ensures that residents have the opportunity to work with these teams. “Our APPs see follow-up patients, thus allowing the residents and attending physicians to see more new patients and acute consults,” she said. “As APPs are now being utilized nationwide due to the physician shortage, it’s helpful for residents to learn how to work alongside APPs, as they will likely continue to work with them in future practice.”

APPs Enhance the Workforce

Majersik and colleagues called on the AAN to include a postgraduate didactic curriculum for APPs—perhaps as part of the APP conference the AAN recently established—and build upon a recently developed online 12-month neurology course aimed at providing foundational knowledge of 8 categories of common neurologic problems.

“This knowledge content could be enhanced with the development of clinical minifellowships in the most common outpatient and inpatient neurologic disorders,” Majersik and colleagues suggested. “The AAN should acknowledge completion of such education with certification or added qualifications to provide assurances of training.”

The report also emphasizes the importance for neurology practices to incorporate team-based care formats that are welcoming to assurances of training.

“...Dr. Nelson and I had to go through the wringer for over a decade to prove our competency—not only just prove it, but to actually gain it. Neurologic disorders are very complicated, and it takes seeing a lot of patients to see what’s out there and to become competent and [take] care of people,” Maloy said.

Nelson concurred, later commenting, “You can’t just walk in and [provide that level of care]. You’ve got to know the physiology and the anatomy in order to figure out the pathology.

“I think it’s actually been proven that the amount of testing that’s ordered by a physician extender compared to an MD or a DO is astronomical, so it’s certainly not saving the system, or certainly the patient, money,” Nelson added, also expressing concern with an APP training in a neurology practice, only to later move on to another setting. “We fully, fully train them to be our extender, and we teach them some neurology...and they quit and they go to the [Department of Veterans Affairs] where they practice completely independently.”

Bernard noted the additional concern of expectations in referring a patient to a neurologist. “When primary care doctors or other specialists refer our patients to a neurologist, we’re counting [on the fact] that the patient is going be seen by an expert who knows more than we do,” she said.

In a viewpoint column in JAMA Neurology, the authors strongly agreed that increased training for advanced practice clinicians (APCs) is essential, as is structuring neurology practices to optimize their function, contribution, and retention. “Exposure to neurology needs to be integrated into APC education by neurologists and neurology APCs, both in the classroom and in clinical experiences,” authors Calli Cook, DNP, APRN, FNP-C, an assistant professor at Nell Hodgson Woodruff School of Nursing at Emory University, and Heidi Schwarz, MD, a professor of clinical neurology at the University of Rochester Medical Center in New York, wrote. The pair encouraged combining onboarding with resident and medical student educational offerings and developing a culture of inclusiveness as possible approaches.

Cook told NeurologyLive® at the time the viewpoint was published that the main advantage APCs bring to the table is their distinct

at their highest level, thus reducing the mismatch,” Majersik and colleagues wrote.

The expansion of neurology practices to incorporate APPs is not universally welcomed, however. Recently, Rebekah Bernard, MD, a primary care physician and coauthor of a book concerned with the increased scope of practice of APPs, Patients at Risk, conducted a podcast interview with Carol Nelson, MD, a neurologist at Avera Medical Group in Sioux Falls, South Dakota, and Alyson Maloy, MD, a neurologist and psychiatrist at Portland Cognitive and Behavioral Neurology in Portland, Maine, who emphasized the extensive training required to provide care to patients with neurologic disorders.

“...Dr Nelson and I had to go through the wringer for over a decade to prove our competency—not only just prove it, but to actually gain it. Neurologic disorders are very complicated, and it takes seeing a lot of patients to see what’s out there and to become competent and [take] care of people,” Maloy said.

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Cook told NeurologyLive® at the time the viewpoint was published that the main advantage APCs bring to the table is their distinct
backgrounds. “In a high-functioning effective team, you want people who have different experiences and are exceptional at those different levels of care. When you hire a PA [physician’s assistant], you may be getting someone who has worked as an EMT [emergency medical technician] or in an ambulance and has that experience that another person on the team doesn’t. When you hire an advanced practice nurse, you have those years of nursing experience and those clinical hours that roll into that person who can help with other things,” she explained.

In considering optimal practice structure, Cook and Schwarz proposed a distributed leadership approach, not only to enhance productivity but also to reduce burnout and help avoid the turnover of APC staffing after the investment in their training. They wrote that distributing leadership—delegating a portion of authority and accountability to those who are working most closely with the patients—is an approach to consider.

Majersik reflected on the debate and indicated that it comes down to the individual practitioner and their particular training. “I would argue that the best headache provider in [Utah] is a nurse practitioner because she’s been doing it for 25 years or more. It’s certain that one fresh out of school probably doesn’t have that expertise. But I think it can be gained,” Majersik said.

“It’s no different, really, for primary care. There’s a huge amount of work required to become an internist. I wouldn’t consider the issues to be any different for neurology than they are for primary care, where you’re supposed to manage all the body systems. So I think it’s a matter of training and knowing who you’re referring to,” she added.

Valuing Neurology and Neurologists

Majersik and colleagues wrote that they considered their third strategy of valuing neurologists and advocating for them to state and federal policy and lawmakers “in many ways the most important,” urging that “advocacy efforts must frame, highlight, and publicize the danger that the mismatch poses to demonstrate the urgent need and looming public health crisis.”

Their report recognizes initiatives of the AAN to increase community knowledge about the mismatch between demand for and supply of neurologists and supports efforts to publicly acknowledge those who are succeeding at reducing the gap. They note, for example, the existence of an AAN joint award to the chair and neurology course or clerkship directors for the top 5 departments garnering the highest percentage of medical students choosing neurology.

The report points to compensation of neurologists as a critical component of addressing this mismatch. “Regrettably, the increasing demand for neurologists is not driving a corresponding increase in the value of neurologists as measured by compensation,” the authors noted.

Majersik and colleagues are hopeful, however, that advocacy for programs such as the 2021 Medicare Physician Fee Schedule increases to work relative value units for evaluation and management codes will provide some correction. They also anticipate that participation in development of alternative payment models will benefit the field.

Majersik also emphasized to NeurologyLive® this need to advocate for the value of neurologists and neurology. “I think we’re also...victims of our own success,” she said. “We now have amazing treatments for multiple sclerosis, epilepsy, and migraine, and all of those are diseases, not just of persons who are [older] but also of those in their productive years. So it has seemed to me that there is more need because we have more to do.

“You want to showcase what a fantastic field it is, what a difference we can make in people’s lives, so that the younger generation sees it as a viable option for them [as a] field to go into.”

For a full list of references, see the article on NeurologyLive.com.
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VYEPTI CAN REDUCE MIGRAINE DAYS AFTER THE FIRST DOSE

Primary endpoint: After a single dose of VYEPTI 100 mg, patients had 23 fewer migraine days, on average, over 3 months.

VYEPTI 100 mg and 300 mg reduced mean MMD 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).

* Calculated by multiplying the mean change from baseline in mean MMD by 3 months.

≥75% MIGRAINE RESPONDER RATES

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.
† This is a key secondary endpoint.
‡ This is a prespecified secondary endpoint, not adjusted for multiplicity.

100% migraine responder rate

35% of patients were migraine-free for a month or more with VYEPTI 100 mg (vs. 22% with placebo during the 6-month study period).

* A migraine-free month was defined as a consecutive 28-day period in which the patient experienced no migraine. 100% reduction was a prespecified secondary endpoint, but not a pre-specified analysis. Therefore, no definitive conclusions should be drawn.

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For more information, please see the Prescribing Information. 1,2

VYEPTI® (eptinezumab-jjmr) injection, for intravenous use

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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. Reactions have included anaphylaxis and 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. Cases of anaphylaxis have been reported in the postmarketing setting. If a hypersensitivity reaction occurs, consider discontinuing VYEPTI and institute appropriate therapy.

ADVERSE REACTIONS

The following clinically significant reactions are described elsewhere in the labeling: Hypersensitivity 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 991 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. 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 hypersensitivity.

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</th>
<th>VYEPTI 300 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=579</td>
<td>N=574</td>
<td>N=588</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Hypersensitivity reactions*</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*Hypersensitivity reactions includes multiple related adverse event terms, such as hypersensitivity, 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.

Immuneogenicity: 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.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of VYEPTI. 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. Immune System Disorders – Anaphylaxis.

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 Data]. 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: Risk Summary - 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.

CLINICAL PHARMACOLOGY

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.

Patients with 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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Stimulation Approaches to Epilepsy Treatment

By Jennifer S. Sun, PhD

**EPILEPSY IS A COMMON CHRONIC** neurological disorder characterized by spontaneous, recurrent, and severe seizures, which greatly diminish quality of life for affected individuals.1,2 Approximately one-third of the 3.4 million US patients with epilepsy currently experience drug-resistant epilepsy.2-4 Thus, novel intervention strategies are urgently needed.3,4

Because epileptogenesis and seizure propagation can be linked to altered cellular ion homeostasis, which reduces the stability of membrane potential, a stimulatory technique can correct for pathologically increased excitability or deficient inhibitory control within the epileptic focus.3 Such deep brain stimulation (DBS) approaches, which have traditionally been applied for neurobehavioral corrections, have increasingly become repurposed for seizure management.1,5

DBS involves the use of an electrical current to activate or inhibit neurons.1 Consequently, cellular membrane polarization is altered, reducing neuronal hyperexcitability and interfering with discharges of epileptogenic networks.1,6 DBS is advantageous because it is reversible, the effects are localized, and the stimulation settings can be dynamically adjusted after device implantation to optimize efficacy and minimize adverse effects (AEs).1 The SANTE study (NCT00101933)7 confirmed both short- and long-term benefits of DBS in reducing seizure frequency, with seizure activity attenuated for up to 5 years.3

Vagus nerve stimulation (VNS) is a form of DBS that was first approved in 1997 for use as an adjunctive therapy in patients with pharmacoresistant epilepsy.8 VNS devices have been successful in reducing seizure frequency, severity, and duration; decreasing antiepileptic drug (AED) use; and improving overall quality of life for patients.8 VNS in the first seconds of a drug-induced seizure successfully aborts the ictal event.2 These devices require minimally invasive surgery to place coiled stimulation leads around the left vagus nerve. The leads are then connected subcutaneously to a generator placed below the clavicle ([FIGURE 1]).2-4 The orientation of the field is important; rotating the orientation of the applied electric field relative to the soma-dendritic axis of the main neuron changes the strength and direction of the effects ([FIGURE 2]).4 VNS devices are beneficial because they can be interrogated and programmed externally after initial implantation and system validation.2 Moreover, VNS devices are well tolerated, with no demonstrable AEs on vagus-mediated visceral functions.5,6,10

Several VNS devices have received FDA approval, including the Neurocybernetic Prosthesis System (Cyberonics, Inc) in 2001,11 the NeuroPace Responsive Neurostimulation System (NeuroPace, Inc) in 2013,12 and Medtronic DBS Therapy for Epilepsy (Medtronic, Inc) in 2018.13 Cyberonics’ VNS therapy system is the most widely used neurostimulator for patients older than 12 years who have intractable partial epilepsy.3,14 NeuroPace’s device is approved for patients older than 18 years who have refractory epilepsy with no more than 2 epileptogenic foci.12 Medtronic’s device is approved as an adjunctive therapy for patients older than 18 years with refractory, partial-onset epileptic seizures.3,11

Clinical trials have demonstrated the safety of VNS and its success in suppressing seizures in humans.2,14 In a 1998 trial, 254 patients were recruited for an evaluation of the Cyberonics’ VNS device in managing epilepsy.2 Inclusion criteria included being aged 12 to 65 years; having had at least 6 medically refractory partial-onset seizures involving alteration of consciousness over 30 days, with no more than 21 days between seizures; and having a stable regimen of 1 to 3 FDA-approved AEDs for at least 1 month before study entry.2

Patients received either high (a 30-second series of pulses, with each pulse lasting 500 µs, delivered at a frequency of 30 Hz every 5 minutes) or low stimulation (a 30-second series of 130-µs, 1-Hz pulses).
every 3 hours). Patients in the high-stimulation group received progressive increases in the current as tolerated (up to 3.5 mA) and were given a handheld magnet with which they could manually activate the device to produce a stimulatory signal when needed to abort a seizure. Patients receiving high stimulation experienced a mean 27.9% decrease in total seizure frequency ($P = .02$) and a reduction in partial-onset seizures ($P = .02$). Patients receiving low stimulation also experienced a reduction of total seizures (average of 15.2% decrease, $P < .0001$) and a reduction in partial-onset seizures ($P < .0001$), although to a lesser extent than the high-stimulation group. Patients in the low-stimulation group experienced improvements to well-being, although the high-stimulation group experienced significantly greater improvement in perceived well-being compared with the low-stimulation group. AEs included vocal cord paralysis, facial muscle paresis, fluid accumulation over the generator, and infection around the device, all of which resolved after treatment or device removal. No changes in serum chemistry, hematology, urinalysis, weight, or vital signs were observed.

Long-term benefits of VNS therapy with Cyberonics’ device were examined in a retrospective review of patient data conducted at New York University Langone Comprehensive Epilepsy Center and Cooperman Barnabas Medical Center. Seizure control improved significantly over time (mean seizure reduction of 35.7%, 52.1%, 58.3%, 60.4%, 65.7%, 75.5%, and 75.5% at 6 months and years 1, 2, 4, 6, 8, and 10, respectively; $P < .01$ for all comparisons) in the 65 enrolled patients, with a plateau after 24 months of therapy. The median number of weekly seizures decreased significantly from baseline (4) to last follow-up (0.5), for an overall mean seizure reduction of 76.3% ($P < .001$). However, an observed increase in AED burden over time may have contributed to the benefit observed in the study.

Use of VNS as an adjunct to best medical practice (BMP) was studied in the PuLS E trial (NCT00522418), an international, multicenter, prospective, randomized, parallel-group, open-label, long-term effectiveness study. Improvements in quality of life were recorded with the widely accepted Quality of Life in Epilepsy 89 (QOLIE-89) item inventory scoring system.

PuLS E was prematurely terminated in July 2008 because of low enrollment, which was attributed to patient resistance to study randomization. Strong preexisting opinions (either positive or negative) about VNS therapy were common, leading many patients to reject study participation because it required random assignment to either BMP plus VNS or the BMP-only control group. Therefore, the planned study duration was reduced from 2 years to 1 year, and the original enrollment estimate of 362 patients was modified; 96 patients (48 in each group) with a baseline QOLIE-89 score and at least 1 post-baseline assessment were evaluated for efficacy (including only 7 patients who completed 2 years of follow-up). Compared with the BMP-only group, patients assigned to VNS plus BMP saw significantly greater improvements in the QOLIE-89 total score ($P < .05$) and seizure frequency ($P = .03$). The difference between the groups increased gradually over time, reaching a maximum at the end of the 12-month follow-up, but differences at the 3-, 6-, and 9-month time points were not statistically significant.

The precise mechanism of action of VNS remains unknown. In humans, VNS alters blood flow within certain brain regions. Some authors have suggested that brainstem nuclei play a role in the vagal antiepileptic mechanism. Preoperative predictors of long-term therapeutic response to VNS remain elusive. Changes in AED regimens are common and may also impact seizure frequency, potentially confounding efforts to determine how much clinical improvement can be attributed to VNS alone. Over time, these AED adjustments may interact synergistically with the effects of VNS to maximize seizure control. Additional research is needed to differentiate between the contributions of factors such as AED changes to the long-term outcomes of patients receiving VNS therapy.

Overall, VNS is an effective and safe nonpharmacologic adjunctive treatment for patients with refractory partial-onset seizures. VNS is not a cure for epilepsy but is designed to lessen the number and severity of seizures. Patients undergoing long-term VNS treatment should be aware of the need for periodic device revisions, most of which involve generator changes due to power depletion after several years of use. A less common reason for revision is lead fracture. Removal of the device is uncommon and often temporary. The efficacy of VNS is also limited; it is comparable to introduction of a new AED. Automation, more effective information processing, and device miniaturization are anticipated improvements.

Suppression of epileptiform activity propagation is also achievable by delivering electrical currents noninvasively using temporal electrodes. The placement of the active electrode (anode) is based on the cortical area to be modulated, whereas the return electrode (cathode) is placed on an unrelated or extracephalic region. Such transcranial electrical stimulation (tES) strategies include the following: transcranial direct current stimulation (tDCS), which uses an anode and cathode to alter excitability and connectivity in the brain; transcranial alternating current stimulation, which uses an anode and cathode to alter excitability and connectivity in the brain; transcranial random noise stimulation.

**FIGURE 3. Oscillation Frequency and Amplitudes Implemented in Noninvasive Brain Stimulation Techniques to Increase Cortical Excitability**
which uses short durations of stimulation to entrain neural oscillations, and transcranial random noise stimulation, which uses an alternating current to stimulate at random frequency and amplitude within a specific range. The mechanism of action of tDCS remains unknown, but studies have determined that functional N-methyl-D-aspartate receptors and sodium and calcium channels are required for tDCS, suggesting that alteration of synaptic function underlies the effects of tES.

tES is beneficial because of its targeted effects on cortical excitability. No severe AEs have been observed with tDCS. In a rodent model of epilepsy, tES was shown to not disrupt sleep or affect waking behaviors. Mild AEs included headache, itching at the site of electrode placement, and fatigue. tES benefits are dependent on the signal amplitude and neural mechanisms, such as stochastic resonance, rhythm resonance, temporal biasing of neuronal spikes, entrainment of network patterns, and imposed patterns. Age, sex, composition of the tissue under the anode, electrode placement, current intensity, current phase, and current frequency may also affect elicited behavioral effects. In rodent models, appropriate timing of tES with brain patterns and activity was determined to be critical for effectively reducing spike-and-wave episodes. Thus, deep-electrode recordings would be required for accurate detection of abnormal patterns prior to tES induction. Moreover, certain drugs, such as the selective serotonin reuptake inhibitor, citalopram (Celexa; Allergan), can interfere with induced inhibition and abolish the effects of tES.

Although numerous animal and human studies have demonstrated successful suppression of epileptiform activity without neurological injury, another major barrier to tES is loss of much of the applied current due to shunting across the scalp caused by the higher resistance of the skull compared with the scalp. Compared with rodents, the larger heads and thicker skulls of primates necessitate a stronger applied current to offset the greater loss to shunting. Thus, investigators translating animal model-based protocols to humans should modify the stimulation parameters as necessary to produce comparable intracerebral fields.

Future studies of tES should include large-scale investigations of optimized electrode placement, ideal stimulation protocols, long-term effects, and strategies for minimizing peripheral and indirect effects. Simultaneous stimulation and brain activity recording will also provide quantitation of tES-induced effects. Also important to investigate are the effects of sensory contributions, such as anesthesia or mood-altering drugs.

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

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Perspectives on the Management of Narcolepsy and Excessive Daytime Sleepiness

Expert neurologist and sleep specialist Chris Winter, MD, provides a practical outlook on the identification and management of narcolepsy and excessive daytime sleepiness.

By Matt Hoffman

Narcolepsy has been a challenging condition for physicians to treat, although advances in clinical care have allowed for a great understanding of the condition and its features. Among the biggest challenges, though, has been the identification of patients. The symptoms of narcolepsy can be easy to recognize once they are noticed, but often, even the cardinal feature—excessive daytime sleepiness—can be difficult to see.

Fortunately, there have been several therapeutic and clinical developments that have made intervening much easier. In a recent NeurologyLive® Insights™ series, Chris Winter, MD, owner of Charlottesville Neurology and Sleep Medicine (CNSM) Clinic and CNSM Consulting, offered up his experience with treating and assessing the sleep disorder, highlighting ways the physician community can address the unmet needs and the current therapeutic options for patients.

Challenges With Differential Diagnosis

The formal diagnosis of narcolepsy can be difficult to reach. Often, it can require an overnight stay at a sleep center for an in-depth sleep analysis by a sleep specialist, with patients providing sleep history and records, and undergoing polysomnography and the multiple sleep latency test. Much of this is in an attempt to rule out other similarly presenting disorders.

“Narcolepsy has been referred to as the ‘great pretender’ because its symptoms often look like different diagnoses, and that’s especially true when you start to divide out the excessive sleepiness that patients with narcolepsy have,” Winter said, adding that there are several other symptoms that can add to the challenge, such as hallucinations and cataplexy. However, there are also symptoms that can introduce difficulty in differentiation because of their broad nature. One such example, Winter said, is depression.

“If you just look at excessive daytime sleepiness and imagine a patient going to a doctor, saying, ‘I’m tired all the time. I don’t want to get out of bed. I fall asleep at work. On weekends I ignore my friends. I ignore my hobbies. I ignore the things that I like to do. All I want to do is spend time in bed sleeping.’ You can imagine that a primary care provider might look at those symptoms and think, ‘Wow, you sound pretty depressed because it’s so difficult for you to really get out of bed and engage in life,’” he said. “There certainly can be depressive elements to that, but what we’re really describing is a person with excessive sleepiness, so depression is high on that list. Individuals who are excessively sleepy often have tremendous difficulties with concentration and focus, so ADHD [attention-deficit/hyperactivity disorder] can jump in there as well, because people can have tremendous difficulty with attention.”

Winter explained that another common symptom is anxiety, as those with excessive daytime sleepiness may rely on anxiety as a tool to stay awake. In these instances, these patients are often disguised as busy people because they avoid sitting still for too long. These symptoms can muddy the diagnostic waters because they hide the underlying symptom of excessive sleepiness, but the challenge does not stop there. Even the more traditional symptoms can cause confusion.

“When you start looking at the hallucinations that people have, when you look at the cataplexy, somebody, when they’re laughing, actually kind of falls over and can’t move for a short period. Now we start getting into the confusion with seizures, confusion with syncopal events or passing out, [and] psychiatric conversion disorders. He’s pretending to have a seizure. He’s pretending to pass out,” Winter said. “Then the hallucinations, hearing things before you go to bed or seeing things, could often be confused for a frank psychosis or a bipolar kind of disorder, where individuals are very depressed or having manic episodes.”

Because of this, patients with narcolepsy often run through the gamut of misdiagnoses before getting the proper one. That delay in diagnosis can last as long as 15 years for some individuals, Winter said, which can ultimately result in worse outcomes. But for Winter, the biggest issue with the misdiagnosis—besides unnecessary medication use—is the great disruption to the quality of life.

“I talked to a patient one time who said, ‘You’re the 13th doctor that I’ve seen for my problem, and if you can’t figure out what’s wrong with me, I’m going to stop seeing doctors,’” he said. “She told me that her problem was that she melted every day, and the melting was cataplexy.
Thus, she was diagnosed with all kinds of problems. To me, the biggest problem is this wasted time or wasted opportunity.”

“That in and of itself is really sad to me. I want people to lead their fullest lives, and this disorder prevents that from happening,” he said.

**Selecting Optimal Therapy for Narcolepsy**

In recent years, a number of therapies have made their way through clinical development into the therapeutic arsenal. Each new option offers more possibilities for patients, making the process of determining which is best for a given individual extremely important. One such factor for deciding on therapy is age, Winter explained.

“We know that oxybates are approved for kids who are quite young. That's a factor,” he said. “Pregnancy is always a factor with any medication, so we want to make sure individuals who could become pregnant or are pregnant understand the different mechanisms of actions of the drugs and the relative risks they carry. Some medications, like oxybate, don't play well with alcohol, so if an individual is known to drink significantly, particularly in the evening—maybe a young grad student who might be prone to more drinking—we want to talk about that as well.”

Another facet for consideration is drug-drug interactions, as some of the available narcolepsy agents interact with other drugs. One such example Winter offered was birth control, as its metabolism can be affected by agents, such as modafinil (Provigil; Cephalon), armodafinil (Nuvigil; Teva), and pitolisant (Wakix; Harmony Biosciences). “We're looking at concurrent psychiatric conditions and the other medications that the patient might be taking for those or other disorders, including depression and anxiety. All those things may predispose the clinician to choose one drug over another,” Winter said.

As Winter put it, one of the “balancing points” with the medications used to treat narcolepsy is that they can occasionally create anxious feelings, jitteriness, or heart rate elevations for patients. These symptoms can be minimal with solriamfetol (Sunosi; Jazz Pharmaceuticals) use, Winter said, making it “another great option in line with drugs like modafinil and armodafinil for individuals to take when they're awake to help them improve or stabilize wakefulness during the day.”

“The final thing I would say is: Do you have a patient who's predominantly type 2 excessively sleepy, or do you have a patient who struggles with sleepiness and cataplexy? If cataplexy is a big feature in a patient's life, we may want to consider a drug like oxybate or pitolisant earlier in the process to get that cataplexy under control,” he said.

**Practical Insight for Community-Based Physicians**

Winter closed the series by providing some advice for community-based physicians on how to address and identify patients with narcolepsy. He began by pointing out some of the current unmet needs and challenges in clinical care, namely, education.

“Challenge No. 1 is getting good information out there to primary care doctors, parents, teachers, school administrators, and school nurses about what narcolepsy looks like and how we can better identify it,” he said. “In other words, if a child always falls asleep during world history class, maybe punishing them isn't what we need to do. Rather, ask some questions, and don't automatically assume it's because the kid is staying up too late playing video games. The same thing could be said for employers. If you've got an individual who's falling asleep a lot at work, rather than firing them or blaming them for some personality fault, sit down with them and say, 'Listen, your coworkers say you're falling asleep at your computer every day. Is everything OK? What's going on?' Point them in the direction of a resource that could help them.”

Once individuals receive a diagnosis, though, the challenge is not immediately resolved. Winter explained that some estimates suggest that the majority of sleep doctors do not feel comfortable diagnosing or treating narcolepsy, and his personal clinical experience has been in line with that. Unfortunately, this can often lead to patients getting diminished or forgotten because of a lack of interest or uncertainty about treatment.

“Misdiagnosis is a big problem, too. It's just a matter of spending the time with the patient to figure out what medication or medication combination is going to work best. That does take some effort, enthusiasm, and time, but from my personal viewpoint, there's nothing more satisfying than discovering and diagnosing a patient with narcolepsy and getting them the wakefulness they need to lead a much more fulfilled and happy life. These are some of the most appreciative patients in my clinic,” Winter said.

Winter offered up 2 main points of advice for community-based providers who see patients with narcolepsy. The first is to always perform a sleepiness evaluation every visit, even for those with an existing diagnosis of narcolepsy. The Epworth Sleepiness Scale “does a great job of it,” he said, adding that it is a valuable tool in discovering those with sleepiness issues.

“Patients with narcolepsy are not great at describing their symptoms, so they tend to underestimate and minimize their symptoms,” he said. “Never trust a patient who has narcolepsy's ability to determine whether they're normal. They're good at telling you they're better or worse, but their great day may be your worst day. Thus, it's very important for us to always screen for excessive sleepiness in all our patients.”

The second main point of advice Winter offered was to refrain from automatically assuming the first-choice medication is going to be the best choice, even if a patient reports feeling better. Again, he advised referring to the Epworth Sleepiness Scale for guidance.

“All medications that we use to treat narcolepsy have a role with a patient, so if you're a provider who said, 'You know what, I only use drugs A and B for narcolepsy. Drugs C, D, E, and F, I don't even bother with,' then you're probably making a bad choice. Drugs C, D, E, and F may not be perfect for everyone, but for individuals who treat a lot of narcolepsy, we find that every one of these medications is meaningful and helpful to somebody. That's really important,” he said.
CHALLENGE-MIG Aims to Optimize Newly Approved CGRP Preventives

The phase 4 study will evaluate the efficacy and safety of once-monthly injectable galcanezumab compared with every-other-day rimegepant taken orally.

By Marco Meglio

RESEARCH HAS SHOWN THAT raised blood and salivary levels of calcitonin gene-related peptide (CGRP) occur in patients with headache disorders, such as migraines and cluster headaches, as well as several neuralgias. The recent discovery of targeting the CGRP pathway has led to a number of new medications, including Eli Lilly’s galcanezumab (Emgality) and Biohaven Pharmaceuticals’ rimegepant (Nurtec ODT).

Announced in July 2021, CHALLENGE-MIG (NCT05127486) is the first head-to-head clinical trial comparing 2 medications targeting CGRP (TABLE). Galcanezumab, a monoclonal antibody (mAb), binds to the CGRP protein, preventing it from attaching to the CGRP receptors, whereas rimegepant blocks the receptor for this protein. The hope is that findings from this multisite, randomized, double-blind, double-dummy, parallel-group phase 4 study may help clinicians and patients make more informed treatment decisions.

The trial opened enrollment in November 2021 and is expected to enroll approximately 700 adults with episodic migraine. The primary end point will be a 50% reduction in monthly migraine headache days for up to 6 months of treatment. Those with a diagnosis of episodic migraine with or without aura will be treated with either 120-mg galcanezumab once-monthly injection with an initial 240-mg loading dose, or 75-mg rimegepant taken every other day.

Galcanezumab was FDA approved in September 2018 as a preventive treatment for migraine in adults and since then, remains the only CGRP mAb that includes response rates of at least 50%, at least 75%, and 100% reduction in monthly migraine headache days in patients with episodic migraine in its FDA-approved labeling. On the other hand, in May 2021, rimegepant became the first medication approved for both acute and preventive therapy for migraine after originally joining the market as solely an acute treatment.

When enrollment was announced, Shivang Joshi, MD, MPH, RPh, a trial investigator and neurologist at Dent Neurologic Institute, in Amherst, New York, said in a statement, “Lilly’s CHALLENGE-MIG study will help us understand how different types of preventive medications may help people achieve the goals that matter most to them. It’s exciting that insights generated in this first-of-its-kind head-to-head trial will be able to spark treatment plan discussions between people with migraine and their health care providers.”

Secondary end points of the trial include greater than 75% and 100% reduction in baseline in monthly migraine headache days and improvements in the Migraine-Specific Quality of Life (MSQ), a 14-item questionnaire designed to measure migraine-specific health-related quality of life by assessing the limitation of daily performance, and the Migraine Disability Assessment (MIDAS), a 5-item questionnaire used to assess headache-related disability in the past 3 months.

Safety, specifically adverse events, will also be recorded in the phase 4 study. To date, the adverse effects reported in clinical studies of galcanezumab include site reactions, such as injection site pain, erythema, and pruritus, as well as hypersensitivity reactions following the administration of the drug. For rimegepant, patients in clinical trials have reported nausea and some rare cases of hypersensitivity reactions. Patients on this drug have also experienced severe hypersensitivity reactions with symptoms such as dyspnea and rash.

As the toolbox of FDA-approved medications has expanded in recent years, the emphasis on treatment optimization and conducting these types of comparative studies has gained more traction. In May 2021, a study conducted by Popoff et al made matching-adjusted indirect comparisons using rimegepant subject-level data and published aggregate-level results from mAb trials.

When matched to the EVOLVE trials (NCT02614183 and NCT02614196; galcanezumab vs placebo; n = 1773), rimegepant was superior to placebo, with a mean difference in monthly migraine day change from baseline of −1.16 (95% CI, −1.80 to −0.52) and was not statistically significantly different from galcanezumab (0.59 [95% CI, −0.13 to 1.32]). Rimegepant also showed superior MIDAS and MSQv2 results compared with placebo in both EVOLVE trials and in the STRIVE trial (NCT02456740; erenumab vs placebo; n = 955), no statistically significant differences from galcanezumab and erenumab (Aimovig; Amgen/Novartis), another FDA-approved medication, regarding MIDAS.

For a full list of references, see the article on NeurologyLive.com.
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Updates to Gene-Transfer Therapy for Neuromuscular Disorders

Advances in technology and research have pushed the field to the brink of a revolutionary era of treatment.

By Crystal M. Proud, MD
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TARGETED GENETIC THERAPIES are revolutionizing the field of neuromuscular medicine. Previously, patients were limited regarding pharmacologic approaches to treatment and relied mainly on supportive care. The inevitable progression of disease led to anticipated trajectories of declining strength and function. But now, new therapeutic strategies are changing this trajectory, providing hope that leaves the future less clearly delineated.

Gene-transfer therapy utilizes a viral vector to deliver a transgene (a single-stranded DNA genome). Administration of the product leads to widespread biodistribution and release of the transgene in cell nuclei, where its promoter drives sustained protein expression. Disorders of loss of protein function are well suited to this therapeutic approach. Although protein expression is modified by the therapy, the individual’s genome is largely unchanged (which is distinct from gene-editing technologies). In the neuromuscular field, gene-transfer therapies have been explored most rigorously in spinal muscular atrophy (SMA) and more recently in Duchenne muscular dystrophy (DMD).

Spinal Muscular Atrophy
Novel therapeutics, including gene transfer, have radically changed life expectancy and functional status for patients with SMA, a neurodegenerative disease resulting from a biallelic deletion/mutation in the survival motor neuron 1 (SMN1) gene. SMN1 directs production of survival motor neuron (SMN) protein, which is essential to maintain the integrity of the motor neuron. Without sufficient protein production, motor neurons irreversibly degenerate, leading to progressive weakness. SMA affects 1 in 11,000 live births and has been a leading genetic cause of infant deaths. The most common and severe phenotype demonstrates symptoms in the first few months of life, including low muscle tone and failure to meet early motor milestones. Patients with this phenotype never achieve independent sitting and usually do not survive past 2 years without treatment.

Onasemnogene abeparvovec
Onasemnogene abeparvovec (Zolgensma; Novartis) is a gene-transfer therapy that is FDA approved in the US for the treatment of children younger than 2 years with SMA. It is made up of an
AAV9 capsid that carries a recombinant single-stranded human SMN transgene. After 1-time intravenous administration, onasemnogene abeparvovec is widely distributed in peripheral and central nervous system tissues as it crosses the blood-brain barrier to target motor neuron nuclei in the anterior horn of the spinal cord. The most common adverse effects (AEs) associated with its use include elevated liver enzymes and vomiting.

The efficacy of onasemnogene abeparvovec has been established in clinical trials, and real-world experience is rapidly evolving. The first clinical trial to demonstrate benefit was the phase 1 START trial (NCT02122952), which began in 2014 and included 15 patients with infantile SMA. At the last follow-up visit 24 months after administration, the mean Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders motor function score in the high-dose cohort was 56.5 points, compared with 5.3 points in the historic comparison. The long-term follow-up study (NCT04042025) includes 13 of the patients enrolled in START, with all 10 from the high-dose cohort alive and free from ventilatory support now more than 6 years after administration. All motor milestones achieved in START have been maintained, supporting durability of efficacy.

Two phase 3 STRIVE trials (STRIVE-US [NCT03306277] and STRIVE-EU [NCT03461289]) examined onasemnogene abeparvovec administration in patients with symptomatic infantile SMA in the United States and Europe. The results demonstrated rapid and sustained increases in motor function scores as early as 1 month following treatment, with clinically meaningful benefits observed regarding survival and motor milestone achievement compared with natural history. SPR1NT (NCT03550599) was an open-label, single-arm, phase 3 study evaluating administration of onasemnogene abeparvovec in genetically diagnosed infants younger than 6 weeks with no observable clinical signs of SMA. There were 29 patients enrolled, and results demonstrated that all patients were alive and free from permanent ventilation as of the last cutoff date. All patients in the cohort of infants with 2 copies of SMN2—who are predicted to likely have a more severe phenotype—were able to achieve sitting without support at the 18-month assessment, including 11 who achieved this motor milestone in an age-appropriate time period. Eight of 15 patients in the cohort with 3 copies of SMN2 achieved the primary efficacy endpoint of standing without support within a normal developmental window. The remaining 7 patients were younger than the age cutoff for this motor skill. Six of 15 patients in the 3-copy cohort also achieved walking alone within the normal developmental time period. The remainder of patients were younger than the age cutoff for this motor skill. The efficacy of early treatment administration in genetically diagnosed but not yet symptomatic infants in this clinical trial supported the efforts for newborn screening programs throughout the United States, many of which have begun implementation.

Future and ongoing studies are addressing intravenous onasemnogene abeparvovec administration in older and heavier patients in the phase 3b SMART trial (NCT04851873). An intrathecal formulation has been evaluated in patients aged 6 to 60 months in the phase 1 STRONG study (NCT03381729), examining patients with SMA who sit but are nonambulatory. This study was placed on clinical hold because of preclinical concerns for dorsal root ganglia toxicity, but the hold has since been lifted. The primary efficacy end point was met, with 92% of patients demonstrating a 3-point or greater increase in the Hammersmith Functional Motor Scale Expanded assessment score at a postbaseline visit. Intrathecal administration in treatment-naïve patients with SMA who have achieved sitting but are nonambulatory and are between ages 2 and 17 years will be assessed in the new phase 3 STEER trial (NCT05089656). The potential for additive benefit with combination or sequential therapy has been considered and is being explored in the RESPOND study (NCT04488133), in which safety and efficacy of nusinersen (Spinraza; Biogen) administration in patients aged 2 to 36 months who have already received onasemnogene abeparvovec is being investigated.

Duchenne Muscular Dystrophy
DMD is a neuromuscular disease for which gene-transfer therapy is also being explored. DMD affects 1 in 3500 male births and is an X-linked disorder characterized by progressive muscular weakness that typically leads to loss of ambulation by aged 13 years, as well as neuromuscular restrictive lung mechanics with respiratory failure and cardiac failure leading to early death, usually by the third or fourth decade of life.

The DMD gene encodes the protein dystrophin, which serves to anchor the actin cytoskeleton to the extracellular matrix and maintains muscle structural integrity during contraction. Patients with DMD have mutations that disrupt the production of full-length dystrophin protein, leading to muscle breakdown and infiltration of the muscle with fat and fibrosis over time. The DMD gene is the largest gene in the body at 14 kb, making it too large to package completely in a viral capsid for gene transfer. Although, the description of a gentleman with a very mild case of Becker muscular dystrophy who was ambulatory at aged 61 years, despite deletion of 46% of the coding region of the DMD gene, invoked consideration of the potential for critical regions of the dystrophin gene. Clinical trial programs have created “micro” or “mini” dystrophin transgenes that include some of these particular critical regions packaged into AAV vectors. Companies exploring this therapeutic strategy have selected different AAV serotypes, unique components of the transgene, and specific promoters for their products. Sarepta, Solid Biosciences, and Pfizer have explored administration of their products in patients with DMD in clinical trials.

SRP-9001
Sarepta’s product SRP-9001 (microdystrophin) was first administered to 4 boys aged 4 to 6 years in the 101 trial (NCT03375164) who demonstrated a mean improvement of 7.5 points in the North Star Ambulatory Assessment (NSAA) over 3 years. This was in comparison to what is known of natural history, whereby NSAA peaks at aged 6 years with a rate of decline of 3 points per year thereafter. The 102 clinical trial (NCT03769116) examined administration of microdystrophin to boys aged 4 to 7 years at enrollment. The biopsy from week 12 post treatment demonstrated 23.8% microdystrophin expression by Western blot. Functional end point data at 48 months...
was examined in the 4- to 5-year-old group as well as the 6- to 7-year-old group. The 4- to 5-year-old boys who received SRP-9001 showed a statistically significant difference in NSAA score at 48 months post treatment compared with placebo. The 6- to 7-year-old boys were randomized for age, but not NSAA score, and were ultimately found to be not well matched at baseline, making comparison of NSAA score at 48 months challenging when examining treatment vs placebo.\(^{21}\)

The next study of SRP-9001, 103 ENDEAVOR study (NCT04626674), began enrollment in December 2020, examining administration of gene transfer with commercially processed material. The study is ongoing and including ambulatory as well as nonambulatory boys. Data for the first 11 boys aged 4 to 7 years at enrollment demonstrated a 55.4% change in microdystrophin expression from baseline by Western blot at 12 weeks post treatment. There was a mean improvement in NSAA score of 3 points from baseline at 6 months in these first 11 boys as well. The most common AEs included vomiting and transaminitis. No clinically relevant complement activation has been observed.\(^{22}\) SRP-9001 301 EMBARK (NCT05096221) is the next phase of Sarepta’s clinical trial program, and is now open for enrollment.

**SGT-001**

Solid Biosciences’ product SGT-001 has been administered at enrollment in the phase 1 IGNITE DMD trial (NCT03368742) including boys aged 4 to 17 years. An interim analysis of the 3 high-dose subjects demonstrated widespread distribution of microdystrophin-positive muscle fibers. The average microdystrophin protein level in subjects in the high-dose cohort via Western blot at day 90 was approximately 10% of normal dystrophin. Differences in NSAA scores over 1 year following treatment were noted relative to trajectories typically seen in natural history. There were improvements in 6-minute walk test distance in both the low-dose and high-dose groups at 1 year.\(^{23}\) A clinical hold that was placed on the trial program after concern for complement activation leading to patient hospitalization has since been lifted. No new drug-related safety findings have been identified and all previously reported serious AEs have fully resolved. The most common drug-related AEs include nausea, fever, and vomiting.

**PF-06939926**

Pfizer’s product, PF-06939926, has been evaluated in a phase 1 clinical trial (NCT03362502) of minidystrophin. Expression of minidystrophin was evaluated at 2 and 12 months post treatment, demonstrating sustained protein expression. NSAA scores demonstrated improvement 1 year after treatment compared with natural history.\(^{24}\) The most common AEs were vomiting, nausea, decreased appetite, and pyrexia. Serious AEs included persistent vomiting resulting in dehydration, acute kidney injury with atypical hemolytic uremic syndrome-like complement activation, and thrombocytopenia with complement activation. The FDA placed a clinical hold on the trial program December 20, 2021, after the death of a patient in the phase 1 study.

Safety remains a priority, and mitigating AEs involves great consideration for immune responses related to gene transfer. Deaths in the ASPIRO clinical trial (NCT03199469) for patients with another neuromuscular disease, X-linked myotubular myopathy, revealed evidence of comorbid hepatobiliary disease at baseline that appeared to increase risk for worsening cholestasis and liver failure, with some fatal liver dysfunction observed in that clinical trial, prompting a clinical hold.\(^{25,26}\) Hepatotoxicity with transaminitis has been most commonly observed in the SMA and DMD programs and appears to be steroid responsive when related to cytolysis rather than synthetic liver dysfunction and failure. To optimize safety, programs have focused on evaluating baseline liver function, ensuring no recent or current infection at the time of drug administration, and administering corticosteroids prior to and following drug administration.

**Conclusion**

Great enthusiasm surrounds the promise of gene transfer therapies, both within and beyond neuromuscular medicine. The efficacy of the SMA gene transfer program has marked a significant milestone in the journey to alter natural history for patients with neuromuscular disease. What was once a goal to just survive has shifted to a focus on how to optimize and thrive. With scientific advancement has also come a respect for the accompanying risk and the unknowns that persist. There is still much to be learned about gene transfer. Setting expectations for potential therapeutic outcomes remains an important consideration as opportunities evolve. In addition, although these pharmacologic strategies change the model of treatment, comprehensive multidisciplinary care remains a core component of the therapeutic strategy for patients with nerve and muscle disease.
Parkinson Disease Subtyping: Are We There Yet?

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Clinicians and researchers have long considered Parkinson disease (PD) to be a neurodegenerative disorder with variable presentations and progression, suggesting that multiple pathophysiologic mechanisms lead to a similar phenotype that we call PD. Its clinical and demographic heterogeneity suggests that if we were able to accurately identify different “types” of the disease, we would be able to better manage patients, understand underlying disease mechanisms, and, potentially, find target-specific neuroprotective therapies.

As we embarked on this challenging journey, initial research focused on clinical characteristics to identify and separate different PD cohorts to allow for better prognosis, information concerning risk of cognitive or mood disorders and rate of disease progression, and, potentially, ability to guide treatment. There is great interest in the use of such a personalized medicine approach in the field as it applies to advanced therapies, such as deep brain stimulation.

Age when symptoms begin commonly is used to subdivide patients into those who experience late- or early-onset PD. Cutoffs are inconsistent among studies, yet most evidence suggests that late-onset PD is linked to more severe tremor, axial symptoms, a lesser motor response to dopaminergic treatment, a greater risk of psychosis, and a substantial tendency for medication adverse effects. Response to advanced therapies has been questioned; reports suggest that patients who are older at time of deep brain stimulation have an increased risk of perioperative delirium and less benefit in quality of life. Conversely, early-onset patients present with a higher prevalence of dystonia, possible higher burden of nonmotor symptoms, and a lower risk of cognitive impairment or dementia. One of the greatest challenges in evaluating age-defined cohorts is a limited ability to assess superimposed or concurrent cerebrovascular disease, musculoskeletal concerns, or Alzheimer disease co-pathology contributing to clinical presentation.

Recently, data-driven approaches have been used to define PD subtypes. Data-driven subtyping takes an unbiased statistical approach to the identification of potential subgroups. Most studies rely on common clinical features that produce different combinations and numbers of subtypes. The differences between results are likely due to cohort characteristics and variables analyzed.
The use of clinical features to separate different motor phenotypes has been studied extensively. The most practical approach divides the patient population into those with tremor and those with predominant axial symptoms; the latter group is labeled the postural instability and gait dysfunction (PIGD), or akinetic-rigid type, phenotype. Patients with PIGD may become less responsive to therapy over time, leading to an increased risk of falls and injury and more rapid disease progression associated with loss of autonomy and institutionalization.5

Studies have used large clinical databases (eg, the Parkinson’s Progression Markers Initiative) to retrospectively identify unique motor subtypes. Five distinct motor subtypes have been proposed based on the motor assessment—tremor dominant (TD), axial dominant, appendicular dominant, rigidity dominant, and postural and instability gait disorder dominant.6 A recent study with short-term follow-up duration identified 3 subtyping categories: mild-motor predominant, intermediate, and diffuse malignant.7 Using a similar approach, our group used long-term data to validate this cluster-based subtyping in a larger PD sample and to extend follow-up to 20 years after diagnosis.8 We observed a similar shift away from TD characteristics and toward those of PIGD. Overall, we found that most patients exhibit changing subtypes with time and eventually fit TD and PIGD subtype classifications. Nonetheless, many questions remain unexplored or have unclear answers.

In general, there is a lack of validation in most data-driven PD subtyping systems, and subtypes are defined based on multifactorial group characteristics. Clinical phenotyping has not been used to identify biomarkers or develop disease-modifying drugs that can help prevent affected individuals from transitioning toward PIGD.

Looking to enrich the current approach, are nonmotor symptoms useful for subtyping?

Nonmotor symptoms (eg, cognitive impairment, autonomic dysfunction, mood disorders) may be the most commonly encountered and, at times, the dominating features in PD. Patients given a diagnosis of PD exhibit clear patterns and differences in these symptoms, which may be valuable in subdividing patient groups or expanding clinical phenotyping. New attempts to classify patients based on their predominant nonmotor symptom(s) are ongoing and may provide more information regarding the pathophysiologic mechanisms of PD.9 This approach is limited, as most patients experience several nonmotor concerns over time, and clinically based approaches possess their own limitations.

Because of these concerns, the suggestion of adding brain imaging to identify specific aberrant neurotransmitter networks and refine subtypes has been entertained. Using this strategy, several classifications have been constructed. The cholinergic or cognitive dysfunction–dominated presentations are best characterized in patients with early cognitive deficit with a tendency for early falls, imbalance, and progression to dementia. Positron emission tomography (PET) studies have suggested cholinergic cortical and systemic (eg, gastrointestinal tract) involvement in early disease.10 Experimental animal evidence suggests an important role of the serotoninergic system in PD. Selective 5-hydroxytryptamine receptor agonists dampen serotonin neuron-derived dopamine release in animals. Several serotoninergic drugs have been investigated in the disease, including some to manage levodopa-induced dyskinesia. Similarly, PET studies using the serotonin transporter ligand carbon C 11 3-amino-4-(2-dimethylaminoethyl-phenylsulfanyl)-benzonitrile support the presence of a specific PD subtype characterized by somnolence, fatigue, and sudden onset of sleep resembling narcolepsy with selective reduction of serotoninergic uptake in the limbic striatum, the raphe area, and/or right insula.11

Finally, a proposed noradrenergic subtype is characterized by focal or generalized dysautonomia, with norepinephrine being the leading neurotransmitter involved. Gastrointestinal dysfunction (eg, delayed gastric emptying, constipation) is the principal manifestation. Additional clinical research is needed to better understand the progression and transition between different nonmotor subtypes. Conceivably, subtypes might converge significantly over time; clinical subtypes are considerably unstable and require modified therapeutic approaches as the disease progresses.

How about genetic subtyping? Where do we stand?

The discovery of monogenetic PD and genetic risk factors presents one of the most logical and intuitive opportunities for subtyping and developing target-specific disease-modifying therapies. There is considerable interest in this area—genetic testing is becoming increasingly affordable, and new initiatives (eg, PD GENERATION) are underway.

The most studied mutations involve GBA and LRRK2. GBA mutations are the most common genetic risk factor for PD harbored by 7% to 10% of affected patients. These patients have an increased risk of cognitive impairment and experience rapid disease progression. LRRK2 mutations result in the most common monogenic form of PD; the clinical phenotype largely resembles sporadic PD except for earlier onset of symptoms, greater lower extremity involvement, lack of cognitive impairment, and lower prevalence of hyposmia and rapid eye movement sleep behavior disorder.

Unique genetic mutations might allow for exploration of unique, specific pathophysiologic mechanisms and biomarkers. With the development of targeted, or gene-specific, interventions, several ongoing clinical trials
are testing molecules that would increase enzyme activity, direct enzyme replacement, replace genes using an adeno-associated virus vector-9, or reduce gene expression. The encouraging results of early studies have demonstrated adequate safety and target engagement. However, certain agents (ie, venglustat) failed to produce any slowing of disease progression.

Denali Therapeutics has developed 2 LRRK2 inhibitors—DNL201 and DNL151—that are in a clinical phase of development with data supporting continued study in patients given a diagnosis of PD. Genetic target–specific therapies may be developed to treat other monogenic forms of PD and sporadic PD in patients demonstrating shared and “modifiable” biomarkers. Some clinical trials targeting GBA or LRRK2 are recruiting patients with PD who do not harbor a genetic mutation.

How can we further classify patients to improve science and clinical care?

We are beginning a new phase of medicine where clinical expertise would rely on novel neuroimaging, genetic, molecular and biomarker techniques to better identify the biological underpinnings of different patient populations as they relate to specific diseases. As we enter this era, a single disease may turn into many, a clinical diagnosis may be considered a “syndrome,” and detailed assessment of biological signatures may be critical to pave the way for individualized medicine. Subtyping would require incorporation of different techniques, definition of new and evolving biomarkers, and, ideally, identification of pathophysiological signatures that strongly correlate with genetic and serum markers that, in turn, may inform our therapeutic approach. Our lack of disease-modifying therapies primarily is a result of our inability to test a homogenous population; motor and nonmotor clinical differences are obvious to health providers caring for patients given a diagnosis of PD. There are several challenges ahead, starting with need to discover biomarkers that would apply to entire populations of patients with this disease. Currently, genetic changes are found only in a small percentage of patients with PD, and this poses a challenge for recruiting participants for gene-targeted trials. The development of simple, noninvasive, inexpensive, reproducible, and reliable biomarkers will contribute to accurate subtyping.

Gut microbiomes, metabolomics, and proteomics are being used to supplement current approaches, and novel neuroimaging techniques are expanding. As the field of pharmacogenomics rapidly grows, differences in drug metabolism may assist in defining and enhancing PD subtyping. There is a need for more extensive use of longitudinal data to expand our understanding of the stability and prognostic value of proposed subtypes. This is particularly important for the incorporation of advanced imaging techniques and artificial intelligence to evaluate and treat this disease. Similarly, data in patients with very early disease, including those with prodromal PD, may provide new insights into the progression and stability of PD symptoms. As science and our understanding of PD subtypes continue to evolve, our community should continue to develop a biologically based definition for this complex disease to inform direct therapeutic implications.

REFERENCES

Addressing US Preventive Services Task Force Aspirin Recommendations for Stroke

In a time when complex medical communication to the public is on display, the need to ensure patient comprehension is of utmost importance for vascular neurologists.

By Daniel Ackerman, MD, FAAN
Vice Chairman, Department of Neurology; Director of Stroke and Vascular Neurology, St. Luke’s University Health Network; Clinical Assistant Professor of Neurology, Lewis Katz School of Medicine

FOR THOSE WHO HAVE BEEN treating patients who suffered a stroke both in and out of the hospital, you are likely familiar with patients who come in and report that they had stopped taking medication for prevention leading up to the time of their stroke. Some report that they just fell out of the habit, and others might have been holding on to medication in anticipation of some surgery or because of an adverse effect. Now, though, we will start to hear a new-old excuse: “I heard it was bad for you.”

A headline in October 2021 stated, “US task force proposes adults 60 and older should not take daily aspirin to prevent heart disease or stroke.” As a board-certified vascular neurologist who frequently recommends aspirin, I was surprised, to say the least. Further reading of the article revealed that a draft recommendation—not finalized—was available for public comment, suggesting that people older than 60 years should not start aspirin for primary prevention but that patients who already take aspirin for a previous heart attack or stroke should not stop unless told to do so by their provider. According to a study quoted in the Washington Post, at least 6 of 10 Americans never get beyond the headline when reading a news story; implying that, unfortunately, important clarifications often go unnoticed.

Heart attack and stroke remain among the leading causes of death and disability in the United States and elsewhere. The best stroke is the one that never happens, and for that reason, a significant amount of time, energy, and resources are used to aid in both primary and secondary prevention of stroke. This is usually accomplished through a combination of anticipation of risk, introduction of lifestyle modifications, and the use of medications. Recently, the United States Preventive Services Task Force (USPSTF) opened for public comment a recommendation against the use of aspirin for primary prevention in certain populations, but this will almost certainly lead to headaches for neurologists treating patients for stroke.
The USPSTF is made up of 16 volunteer members who are nationally recognized experts in prevention, evidence-based medicine, and primary care. Their fields of practice and expertise include behavioral health, family medicine, geriatrics, internal medicine, pediatrics, obstetrics and gynecology, and nursing. Note that there are no neurologists—a fact that we should aim to address. The USPSTF mission “is to improve the health of people nationwide by making evidence-based recommendations on clinical preventive services and health promotion in primary care settings.” The USPSTF was initially established in 1984, but its mandate has evolved over the years; today, insurers are required to cover preventive services that receive a high recommendation from the USPSTF.

Considering the prevalence of cardiovascular disease and stroke among the US population, the focus for some of the task force’s recent recommendations is not surprising. The last finalized guidance from the USPSTF regarding aspirin for primary prevention of heart attack and stroke was in 2016, when it concluded that for people aged 50 to 59 years who have at least a 10% risk of cardiovascular disease (CVD) over the next 10 years, aspirin is recommended for primary prevention. And for people aged 60 to 69 years, life expectancy and risk for complications should be considered and the decision individualized with their physician. There was insufficient evidence to make any recommendation for those younger than 50 years or older than 69 years.

With this most recent proposed revision—that at the time of this writing remains unfinalized—patients aged 40 to 59 years with more than a 10% risk for CVD over 10 years should have a conversation with their physician about aspirin for an individualized decision, taking bleeding risk into account; however, for those 60 years or older, aspirin should not be started for primary prevention of stroke or heart attack because the

### TABLE. Guidelines for Primary Prevention of Stroke

<table>
<thead>
<tr>
<th>Organization</th>
<th>Population</th>
<th>Recommendation</th>
<th>Grade/level of evidence</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPSTF</td>
<td>Adults aged 50 to 59 years who have a ≥10% 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of ≥10 years, and are willing to take low-dose aspirin daily for ≥10 years</td>
<td>Initiate low-dose aspirin use for the primary prevention of CVD and CRC.</td>
<td>B</td>
<td>2016 (being revised)</td>
</tr>
<tr>
<td>USPSTF</td>
<td>Adults aged 60 to 69 years who have ≥10% 10-year CVD risk. (Those who are not at increased risk for bleeding, have a life expectancy of ≥10 years, and are willing to take low-dose aspirin daily for ≥10 years are more likely to benefit.)</td>
<td>The decision to initiate low-dose aspirin use is an individual one.</td>
<td>C</td>
<td>2016 (being revised)</td>
</tr>
<tr>
<td>USPSTF</td>
<td>Adults ≥40 years who are at higher risk for heart disease, have no history of heart disease or stroke, and are not already taking daily aspirin</td>
<td>Have a conversation with their clinician to determine whether they are at higher risk for developing heart disease or stroke and, if so, whether taking aspirin is right for them.</td>
<td>C</td>
<td>2021 (not finalized)</td>
</tr>
<tr>
<td>USPSTF</td>
<td>Adults ≥60 years who do not have a history of heart disease or stroke, and are not already taking daily aspirin</td>
<td>Recommends against initiating low-dose aspirin use for the primary prevention of CVD</td>
<td>D</td>
<td>2021 (not finalized)</td>
</tr>
<tr>
<td>AHA/ASA</td>
<td>Adults aged 40-75 years</td>
<td>Clinicians should routinely assess traditional cardiovascular risk factors and calculate 10-year risk of ASCVD by using PCEs.</td>
<td>COR 1, LOE B-NR</td>
<td>2019</td>
</tr>
<tr>
<td>AHA/ASA</td>
<td>Adults aged 40-70 years who are at higher ASCVD risk but not at increased bleeding risk</td>
<td>Low-dose aspirin may be considered for the primary prevention of ASCVD.</td>
<td>COR 2B, LOE A</td>
<td>2019</td>
</tr>
<tr>
<td>AHA/ASA</td>
<td>Adults &gt;70 years</td>
<td>Low-dose aspirin should not be administered on a routine basis for the primary prevention of ASCVD</td>
<td>COR 3, LOE B-R</td>
<td>2019</td>
</tr>
<tr>
<td>AHA/ASA</td>
<td>Adults of any age at increased risk of bleeding</td>
<td>Low-dose aspirin should not be administered for the primary prevention of ASCVD.</td>
<td>COR 3, LOE C-LD</td>
<td>2019</td>
</tr>
<tr>
<td>AHA/ASA</td>
<td>Patients with a stroke or TIA caused by 50%-99% stenosis of a major intracranial artery</td>
<td>Recommends full-dose acetylsalicylic acid in preference to warfarin</td>
<td>COR 1, LOE B-R</td>
<td>2021</td>
</tr>
<tr>
<td>AHA/ASA</td>
<td>Patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%-99%) of a major intracranial artery</td>
<td>It is reasonable to add clopidogrel 75 mg per day to acetylsalicylic acid for up to 90 days.</td>
<td>COR 2A, LOE B-NR</td>
<td>2021</td>
</tr>
<tr>
<td>AHA/ASA</td>
<td>Patients with recent (within 24 hours) minor stroke or high-risk TIA and concomitant ipsilateral &gt;30% stenosis of a major intracranial artery</td>
<td>The addition of ticagrelor 90 mg twice per day to aspirin for up to 30 days may be considered.</td>
<td>COR 2B, LOE B-NR</td>
<td>2021</td>
</tr>
<tr>
<td>AHA/ASA</td>
<td>Patients with stroke or TIA attributable to 50%-99% stenosis of a major intracranial artery</td>
<td>The addition of cilostazol 200 mg/day (typically dosed 100 mg twice/day) to aspirin or clopidogrel may be considered.</td>
<td>COR 2B, LOE C-LD</td>
<td>2021</td>
</tr>
</tbody>
</table>

AHA, American Heart Association; ASA, American Stroke Association; ASCVD, atherosclerotic cardiovascular disease; CRC, colorectal cancer; CVD, cardiovascular disease; LOE, level of evidence; PCE, pooled cohort equations; RCT, randomized controlled trial; TIA, transient ischemic attack; USPSTF, United States Preventive Services Task Force.

*Grade/level of evidence: USPSTF—Strength of recommendation is graded as follows: “A” recommends with high certainty that the net benefit is substantial, “B” recommends with high certainty of a moderate net benefit or a moderate certainty that the net benefit is moderate or substantial, “C” recommends selectively based on professional judgment and patient preference. There is at least moderate certainty of a small net benefit. “D” recommends against using with at least moderate certainty that there is no net benefit or that the harms outweigh the benefits, and “I” indicates that current evidence is insufficient to assess the balance of benefits and harms. AHA/ASA—All recommendations have a COR that corresponds to the strength of the recommendation from 1 to 3 and an LOE indicating the quality of the evidence behind a recommendation from A to C expert opinion (EO). Class 1, strongly recommends; class 2a, moderately recommends; class 2b, weakly recommends; class 3, moderately strong suggestion of no benefit; class 4, strongly recommends against. AHA, high-quality evidence from multiple RCTs, meta-analysis of high-quality RCTs, or multiple RCTs with corroboration by high-quality registry studies; LOE B-R, moderate evidence from 1 or more RCTs or a meta-analysis of multiple moderate-quality RCTs; LOE B-NR, moderate quality from 1 or more nonrandomized trials or a meta-analysis of such data; LOE C-LD, randomized or nonrandomized observational or registry studies with limitations, meta-analysis of such data, or physiologic/mechanistic human studies; LOE C-EO, consensus of expert opinion.
task force’s review of the evidence suggests that the risk outweighs the benefit. Importantly, this may not apply in the same way for patients who have a history of transient ischemic attack or significant carotid, coronary (without heart attack), or peripheral artery disease. We will need to wait for the final recommendation and explanation of the evidence for further clarification.

Unfortunately, with reporting like the aforementioned headline, those who provide guidance on secondary prevention of stroke can anticipate that patients who have been taking aspirin for secondary prevention will stop, placing themselves at higher risk for a new cerebrovascular event. Joshua Z. Willey, MD, an associate professor of neurology at Columbia University Vagelos College of Physicians and Surgeons and an attending neurologist for the Stroke Service at NewYork-Presbyterian Hospital in New York City, was quoted in a recent article in Neurology Today, saying, “Within 12 hours of a prominent displayed New York Times article on the new thinking on aspirin, I had about 20 messages from patients asking if they should stop taking their aspirin.”

Furthermore, this comes at a time when our recommendations for antiplatelet medications for secondary stroke prevention are becoming more complex rather than less, with expanded options and important stipulations on time of treatment (TABLE). Many of us may remember an increased need to answer questions and concerns about the benefits of aspirin for secondary stroke prevention following the release of the 2016 USPSTF recommendation. Although this may not be a new issue, with the adjustment of the recommendation and considering headlines like the one referenced previously, it is crucial that we take this opportunity to communicate with our patients as well as our hospital colleagues and those in primary care to help limit the risk of patients inappropriately stopping their secondary prevention medications.

So how do we do that?

Be Prepared
Being familiar with these recommendations as well as the recommendations from the American Heart Association/American Stroke Association on both primary and secondary prevention will go a long way toward being able to answer questions about which patients should be treated.

Be Clear
Ensure that your communication about this topic is clear and concise. Improved open communication between providers and patients has never been more important. To preserve patient autonomy, we need to have a simple and understandable message to help empower patients to make informed decisions about their care.

Be Curious
Office staff can be scripted to ask patients during visit preparation if they are aware of the new recommendations or if they have any concerns about their current medication for secondary stroke prevention. It is possible that those who are reluctant to continue their medication may also be more reluctant to talk with you about their concerns. This may also be the population most likely to quickly, and incorrectly, conclude that they no longer should take aspirin for stroke prevention.

Be Proactive
Consider reaching out directly to patients with a message describing and clarifying this recommendation and reinforcing that they should continue their current regimen for now and contact the office with any concerns. This is a great way to leverage the communications capabilities of the electronic medical record.

Be Available
Primary care teams and hospitals that refer patients to your practice may also need guidance regarding how to apply these recommendations in the setting of so many specific caveats and in the face of the ever-present level C evidence. Expert opinion is sometimes the hardest to adjust, regardless of the evidence behind a new recommendation. Communicating through a letter, email, or other means and reinforcing an open pipeline for communication will help clarify best practices regarding stroke prevention for individual patients.

Recommendations can and should change over time. As the quality and quantity of specific evidence grows, we can expect that best practices will continue to be a moving target. A new and important challenge for health care providers, however, is broad-based dissemination of information with limited clinical accuracy. Headlines look to stimulate readers to investigate further, but a push for sensationalism can have important unintended consequences when misinterpreted by patients. By following the principles discussed here and staying ahead of the information curve, we will be positioned to provide counsel, guidance, and reinforcement to help our patients avoid being 1 of the nearly 200,000 people in the United States every year with a recurrent stroke.

REFERENCES
RESEARCH REWARDS

AAN Awards Monica M. Diaz, MD, MS, Clinical Research Training Scholarship
In December 2021, the American Academy of Neurology (AAN) granted Monica M. Diaz, MD, MS, assistant professor in the Department of Neurology at the University of North Carolina School of Medicine in Chapel Hill, a Clinical Research Training Scholarship to support her research project, “Neurofilament light as a marker of synaptic loss in cognitively impaired older people with HIV.” For the project, Diaz will receive a total of $150,000, with $65,000 allotted each year for 2 years, in addition to a $10,000 stipend each year. Diaz aims to identify novel methods of in vivo detection of neurodegeneration in older, cognitively impaired adults with HIV. “I am thankful to the AAN for this award and for the local mentor and departmental support I receive. This award will allow me to continue to develop my career as a clinician-scientist in neurological complications of HIV,” Diaz said in a statement.

Glenda Halliday, PhD, Receives Robert A. Pritzker Prize for Leadership in Parkinson’s Research
At its Research Roundtable event in October, the Michael J. Fox Foundation for Parkinson’s Research (MJFF) awarded Glenda Halliday, PhD, Australian National Health and Medical Research Council Leadership Fellow at The University of Sydney, the 2021 Robert A. Pritzker Prize for Leadership in Parkinson’s Research. Halliday’s work has contributed to findings related to cellular pathways and processes in Parkinson disease (PD), with her overarching interests focused on pathological changes in the disease. Her work aims to identify new intervention approaches to halt, slow, or prevent disease progression in patients with PD. The award from MJFF recognizes scientists’ achievements and contributions to PD research, as well as a commitment to mentoring future PD scientists. Awarded annually since 2011, the prize includes a $100,000 research grant for recipients.

ALS Association Awards a $620,000 Grant to Packard Center for ALS Research
A $620,000 grant was awarded to the Packard Center for ALS Research at Johns Hopkins, the ALS Association announced in December 2021. The grant will support the Answer ALS Data Portal, which was launched in January 2021 to provide open access to amyotrophic lateral sclerosis (ALS) data, which comprise in-depth clinical profiles and big data multomics, that were collected from more than 1000 patients with ALS as well as healthy control participants. Designed to allow researchers to browse data with ease, the portal is a resource for experts to search, filter, and download relative information. “This portal provides researchers from around the world access to clinical data linked with molecular data to better understand the underlying biology of the disease,” Neil Thakur, PhD, chief mission officer of the ALS Association, said in a statement. “Studying [these] data allow us to understand the different subtypes of this complex disease and find new therapeutic targets and pathways to test in the future.”

AFA Marks 20th Anniversary With Grant to Feinstein Institutes for Medical Research
In 2022, the Alzheimer’s Association of America (AFA) celebrates its 20th anniversary and is kicking off the year by announcing a $998,156 grant to be awarded to the Feinstein Institutes for Medical Research. The grant will fund research efforts to develop safe and effective treatments for hallucinations, delusions, and aggression associated with Alzheimer disease (AD). The new 5-year grant will help build on previous research efforts funded by a $500,000 AFA grant awarded in 2016. Investigators, led by Jeremy Koppel, MD, codirector of the Litwin-Zucker Research Center at the Feinstein Institutes for Medical Research, in Manhasset, New York, identified an association between abnormal tau protein distribution in patients with AD, with future research aimed at targeting symptoms of psychosis and aggression by developing immune therapies in the form of antibodies that will bind to pathogenic tau. “The funding provided by AFA made our work possible, and the ongoing support is critical, allowing us to do the necessary research to translate these discoveries into safe and effective treatments for patients and caregivers,” Koppel said in a statement.

AT THE HELM

Elad I. Levy, MD, Is Named President-elect of the Congress of Neurological Surgeons
The Congress of Neurological Surgeons (CNS) announced in January that they had named Elad I. Levy, MD, president-elect. Levy is a professor of neurosurgery and radiology, chair of the Department of Neurosurgery, and the L. Nelson Hopkins III, MD, Professor and Chair of the Department of Neurological Surgery at the Jacobs School of Medicine and Biomedical Sciences at the University of Buffalo in New York. Levy previously served as secretary for the CNS Executive Committee, and his presidential term will begin when he receives the gavel on October 12, at the conclusion of the 2022 CNS Annual Meeting in San Francisco, California. In addition to his contributions as a clinician, researcher, and affiliate, Levy is codirector of the Stroke Care Center and cerebrovascular surgery at Kaleida Health, as well as director of endovascular stroke treatment and research medical director of neuroendovascular services at Gates Vascular Institute.
Explore MS Website

Managing the neuroinflammation of today may help slow the irreversible neurodegeneration of tomorrow.

Visit the MS website to explore early MS neuropathology, disease progression, and patient perspectives through interactive tools that span the spectrum of MS.

**Truths vs Myths**

**Truths and Myths of MS**
Challenge your understanding of MS in this game that includes questions on the diagnosis, management, and some needs of patients with MS.

**Disease Progression in MS**
Explore this case example of RRMS illustrating how early neuroinflammation may progress to irreversible neurodegeneration and clinical disease progression over time.

**Immunoglobulins in MS**
View this PDF to learn about the role of immunoglobulins in patients with MS.

**Mechanism of Disease in MS**
Early neuropathology
Explore how autoreactive immune cells trigger early neuroinflammation in MS.

MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.