As the year 2017 comes to a close, we reflect on many advances in neurology. The emergence of new drugs and devices will provide neurologists with additional therapeutic options to optimize the care provided to our complex patient populations. Antibody therapies are flooding the landscape in nearly every discipline of medicine, and neurology is no exception. As such, 2018 will be an exciting year as we watch many treatments in clinical trials gain FDA approval for use, and additional therapeutic target-based interventions enter the pipeline.

—Paul Mathew, MD, Chief Medical Editor

Forward Thinking: Advances in Neurology

A review of notable neurological developments in 2017 and a preview of the year ahead.

EPILEPSY

NOTABLE DEVELOPMENTS IN 2017

Advances in Neurostimulation

Neurostimulator devices have gained traction in 2017, evidenced by regulatory developments and compelling new data highlighting their utility in the management of epilepsy. In June, the FDA approved LivaNova’s Vagus Nerve Stimulation (VNS) Therapy Programming System, a minimally invasive treatment designed to prevent seizures before they start, in patients as young as four years of age with partial-onset refractory seizures. Several months later, the company received approval for its next-generation VNS device for drug-resistant epilepsy and its SenTiva implantable device, allowing for guided and scheduled programming.

Brain-responsive neurostimulation has also earned wider recognition for the reduction of seizures. Studies presented at the American Academy of Neurology (AAN) Annual Meeting in April offered long-term perspective on the efficacy and safety of brain-responsive neuromodulation in patients with medically intractable mesial temporal lobe epilepsy and in patients with medically intractable seizures arising from eloquent and other neocortical areas.

In the October edition of Practical Neurology magazine, Barbara C. Jobst, MD, Professor of Neurology at Dartmouth-Hitchcock Medical Center in Lebanon, NH, noted that these recent advances are making surgery less daunting from the standpoint of invasiveness. She emphasized that the onus is on physicians to ensure that patients receive optimal treatment. “Given the high proportion of patients with refractory epilepsy for whom adequate care is too often delayed, it is our duty to direct patients to the appropriate providers if we cannot offer the level of care required,” Dr. Jobst wrote.

Expanded Indications for Numerous Anti-Epileptic Drugs

The therapeutic armamentarium for epilepsy was given a boost with new approvals and indications for several drugs. Briviact (briveracetam, UCB) was approved as a monotherapy in patients ages 16 years and older. It is the newest antiepileptic drug in the racetam class of medicines and demonstrates a high and selective affinity for synaptic vesicle protein 2A in the brain.

Qudexy XR (topiramate, Upsher-Smith) Extended-Release Capsules received two new supplemental indications, for use as prophylaxis of migraine headache in adults and adolescents 12 years of age and older. Aptiom (eslicarbazepine acetate, Sunovion) was approved in patients between the ages of four and 17 based on FDA guidance that permits the extrapolation of adult data to support pediatric use.

SUDEP In Focus

The AAN and the American Epilepsy Society have released a new joint guideline for sudden unexpected death in epilepsy (SUDEP), recommending that health professionals tell people with epilepsy that controlling epileptic seizures and seizures in general may reduce the risk of SUDEP. Also endorsed by the International Child Neurology Association, the guidelines were the result of a review of all available evidence showing that general tonic-clonic seizures represent a major risk factor for SUDEP.

According to Michelle Dougherty, MD, Assistant Professor of Neurology and Director of the neurology residency program at the Drexel Neuroscience Institute in Philadelphia, significant knowledge gaps remain when it comes to SUDEP and physicians should take the opportunity to educate
patients and families. “Ideally, a discussion of SUDEP risk and factors that influence risk could help patients and families take appropriate steps to lower that risk wherever possible, such as adherence to prescribed anti-epileptic drugs, continuing to pursue further treatments, and avoiding known seizure triggers,” she wrote in the July/August edition of Practical Neurology® magazine.

Cannabidiol Reaches Late Preapproval Stages

In October, GW Pharmaceuticals completed its rolling new drug application to the FDA for Epidiolex (cannabidiol) for the treatment of Lennox-Gastaut Syndrome and Dravet syndrome. The application was based on compelling Phase 3 findings showing that cannabidiol reduces seizure frequency and is well tolerated. GW Pharmaceuticals CEO Justin Gover, in an interview with Practical Neurology® earlier this year, noted that the company has been diligent in both the development and evaluation of its novel agent. “This is a development program in which there has been a true appropriate response to the level of interest and the level of need to develop something that can meet the stringent requirements of the FDA and provide meaningful important therapy to patients,” said Mr. Gover. “Our job now as a company is to do the right thing by the product, make sure that we present a compelling case to the FDA, and have a team that can launch this and manufacture it appropriately.”

ON THE HORIZON:

Epilepsy therapeutics took many small steps forward this year and is poised for potentially significant growth in 2018, particularly with the possible approval of the first-in-class cannabidiol agent. The field will also continue to evolve with wider prominence of surgical and imaging technologies, according to Michael Sperling, MD, Professor of Neurology and Director of the Comprehensive Epilepsy Center at Thomas Jefferson University in Philadelphia. “Increasing adoption of laser interstitial ablation will modify the practice of epilepsy surgery, as minimally invasive procedures are utilized in new ways.” In addition, Dr. Sperling observes, “genetic testing and autoimmune testing will both become increasingly utilized, and more patients will be diagnosed with these conditions.”

MOVEMENT DISORDERS

NOTABLE DEVELOPMENTS IN 2017
Options Increase for the Reduction of Levodopa OFF Time

The Parkinson’s disease treatment market grew modestly in 2017, led by Gocovri (amantadine, Adamas Pharmaceuticals), the first medicine approved for the treatment of dyskinesia in patients with Parkinson’s disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications. Gocovri is taken once-daily at bedtime and delivers consistently high levels of amantadine from the morning and throughout the day when dyskinesia occurs.

In an interview with Practical Neurology® magazine earlier this year, Rajesh Pahwa, MD, Laverne & Joyce Rider Professor of Neurology at the University of Kansas Health System, noted the significance of the approval by describing challenges of managing dyskinesia in the long-term treatment of Parkinson’s disease. “Right now, our patients are being undertreated for Parkinson’s disease,” said Dr. Pahwa. “Many physicians are hesitant to increase the levodopa dose because it increases the likelihood of dyskinesia. By reducing levodopa, we used to pay the price by increasing OFF time, however with the 274mg once-daily dose of Gocovri we have seen consistent results across three studies that we can reduce dyskinesia and OFF time,” Dr. Pahwa explained.

Another addition to the Parkinson’s disease medicine chest is Xadago (safinamide, Newron Pharmaceuticals). It was approved in March as an add-on treatment for patients with Parkinson’s disease who are currently taking levodopa/
carbidopa and experiencing OFF episodes. In a clinical trial, patients receiving safinamide in addition to levodopa experienced a reduction in OFF time and better motor function scores during ON time than before treatment.

**New Approvals in Huntington’s Disease, Tardive Dyskinesia**

Among the most significant approvals in the movement disorder spectrum were those for rare conditions. In April, the FDA approved Austedo (deutetrabenazine, Teva Pharmaceuticals) tablets for the treatment of chorea associated with Huntington’s disease, making it just the second product approved for the disease. Jill Giordano Farmer, DO, MPH and Leonel Estofan, MD discuss the broader spectrum of Huntington’s disease in the Movement Disorders Focus entry in this issue. Turn to page 45 to read more.

Austedo was also approved for the treatment of tardive dyskinesia, along with Ingrezza (valbenazine, Neurocrine). In the June edition of *Practical Neurology* magazine, Laxman Bahroo, DO, Associate Professor of Neurology at Georgetown University, and Rita Gandhy, MD, MPH, a neurologist at the Parkinson’s Institute and Clinical Care Center in Sunnyvale, CA, noted that the approval of two new agents represents a significant step and will increase awareness for tardive dyskinesia. These agents also allow treatment of tardive dyskinesia without altering the psychiatric medication and potentially worsening mental health. “This changes the treatment options of tardive dyskinesia from reduction, removal, or trial and error options, to a focused option that can be added on to existing psychiatric medications,” Drs. Bahroo and Gandhy observed. Nevertheless, they wrote, challenges persist regarding management. “Given the paucity of treatment options for so long, the availability of tardive dyskinesia-specific treatments poses new challenges about access, cost, and overcoming physician apathy.”

**ON THE HORIZON**

As new entrants to the Parkinson’s disease treatment field will help patients achieve more balance in ON versus OFF time, budding research investigating the etiology of the disease may in the future produce more targeted therapies aimed at disease modification. According to Kathleen M. Shannon, MD, Detling Professor and Chair of Neurology at the University of Wisconsin, Parkinson’s disease research will see an increased emphasis on intracellular protein dynamics, including therapies that will target protein aggregation, “either harnessing the immune system to assist with removal of aggregates or enhancing intracellular mechanisms of protein removal.” Additionally, says Dr. Shannon, there will be a greater focus on experimental therapeutics in prodromal disease (e.g., the asymptomatic gene carrier state in conditions such as Huntington’s disease or the premotor period in Parkinson’s disease), with a new emphasis on biomarkers as outcome measures.

Genetics will also continue to be a major focus of research, according to Dr. Shannon, with “new approaches that alter gene expression (e.g., small interfering RNA or antisense oligonucleotides to reduce protein synthesis for polyglutamine diseases or gene editing using CRISPR technology.” In addition, Dr. Shannon expects remote technologies to play a central role in Parkinson’s disease research and therapeutic management, “either by telemedicine or wearable or other remote technology to better tailor therapies as well as to use as outcome measures.”

**ALZHEIMER’S DISEASE**

**NOTABLE DEVELOPMENTS IN 2017**

No other area of neurology has seen such a prolonged dearth of new medications as has defined the Alzheimer’s disease landscape over the last two decades. Moreover, there are no approved drugs targeting the underlying pathology and slow the progressive cognitive and functional decline of Alzheimer’s disease. Developments this year, however, offer a glimpse of a potentially brighter future.

Aducanumab (Biogen), a monoclonal antibody directed
against several forms of amyloid protein, continues to show promise in slowing the rate of clinical decline in patients with Alzheimer’s disease. In August, the company shared data from a long-term extension of its ongoing Phase 1b trial indicating that in patients treated up to 36 months, amyloid plaque continued to decrease in a dose- and time-dependent manner. Aducanumab is also under evaluation in two global trials, ENGAGE and EMERGE, which are evaluating its impact on cognitive impairment and progression of disability, as well as safety.

Another agent showing promise is the oral anti-amyloid agent tramiprosate, also known as ALZ-801 (Alzheon), which was recently granted fast-track status by the FDA. Phase 3 findings showed that tramiprosate may offer cognitive and functional benefits to patients with mild disease. Researchers found that the cognitive effect of tramiprosate in patients with mild disease increased significantly with time, suggesting a potential disease-modifying effect.

**Imaging Biomarkers**

Beyond therapeutics, scientific inquiry into Alzheimer’s disease has increasingly emphasized the search for reliable biomarkers, and ever-refined imaging tools are bringing the field closer to earlier diagnosis. In the June edition of *Practical Neurology* magazine, Ronald C. Petersen, MD, PhD, Professor of Neurology at the Mayo Clinic, noted that ongoing advances in the biomarker field are carving out new paths in the diagnosis of the disease and development of potential disease-modifying therapies. “Now we’re able to do PET scanning for the tau protein, which comprises the neurofibrillary tangles,” Dr. Petersen wrote. “This enables us an opportunity to actually determine whether a living person has the underlying biologic features that define Alzheimer’s disease, namely, the presence of the amyloid plaques and the presence of the tau tangle.”

**ON THE HORIZON**

As technologies continue to evolve, the possibility of early diagnosis is becoming more concrete. This will ultimately lead to deeper understandings of the disease and possibly offer clues for developing disease-modifying therapies, according to Jeffrey Cummings, MD, ScD, Director of the Cleveland Clinic’s Lou Ruvo Center for Brain Health in Las Vegas. “Alzheimer’s disease is increasingly recognized to have a long preclinical phase that lasts up to 15 years, followed by a prodromal phase with mild cognitive impairment lasting approximately five years,” Dr. Cummings explains. These are the predecessors of the dementia phase where Alzheimer’s disease is traditionally diagnosed with cognitive and functional impairment, according to Dr. Cummings. “Clinical trials increasingly focus on the preclinical and prodromal phases of the disease with the intention of interrupting the process before the brain is severely damaged. These new trials are expected to usher in a new approach to care where biomarkers will identify patients at high risk for progressing to Alzheimer dementia, and therapy will be initiated in the pre-dementia phase of the illness.”

**MULTIPLE SCLEROSIS**

**NOTABLE DEVELOPMENTS IN 2017**

Arguably the most significant drug approval in the field of neurology in 2017 was that of Ocrevus (ocrelizumab, Genentech/Roche). Approved in March for the treatment of both relapsing and primary progressive forms of multiple sclerosis (MS), ocrelizumab is a humanized antibody that targets the CD20 marker on B lymphocytes. It is the first drug approved for the treatment of primary progressive MS. Phase 3 data from the OPERA and ORATORIO trials showed significantly lower annualized relapse rates and percentages of patients with disability progression.

In the April 2017 edition of *Practical Neurology* magazine, Logan Schneider, MD, notes: “With more fundamental neuroanatomic and physiologic understanding of the mechanisms of sleep, targeted therapies are being devised that will address symptoms based on their underlying pathobiology. New medications, such as JZP-110 and pitolisant, are examples of how therapies are taking advantage of novel and specific mechanisms to address sleep-wake issues. Interactions between neurologic/medical diseases and sleep are also being discovered. For example, the dopaminergic aspects of the circadian system tie the story of PD and sleep-wake disruptions together. Discoveries about sleep health and dementia pathology are pointing to mechanisms that have bidirectional influence. With a deeper understanding of the interplay between sleep and disease we may screen, course correct, or even prevent disease to some degree.”

—Logan Schneider, MD
zine, Patricia K. Coyle, MD, Professor of Neurology and Vice Chair of Clinical Affairs at Stony Brook University in New York, noted that ocrelizumab is a high-efficacy agent that’s not only extremely well tolerated but also comes with a favorable dosing schedule, making it a unique addition to the treatment armamentarium. “The patient is going to an infusion center for a couple of hours, two days out of the year, which is both convenient and ensures adherence.”

In primary progressive MS, Dr. Coyle observed that the benefits appear to be predominantly upfront, demonstrating an anti-inflammatory impact as opposed to documenting a true effect on neurodegeneration. Nevertheless, she noted that the mere presence of a therapy for this condition is a much-needed boost. “We have not yet had a disease-modifying therapy for a pure progressive form of MS, which makes the approval of any agent a huge psychological benefit for patients and physicians alike,” Dr. Coyle wrote.

In other MS-related therapeutic news, the FDA approved two generic versions of glatiramer acetate from Mylan, including a three-times weekly 40mg/mL formulation and a once-daily 20mg/mL formulation. As part of its Abbreviated New Drug Applications, Mylan submitted side-by-side analyses, including characterization data, demonstrating that its formulations have the same active ingredient, dosage form, route of administration, and strength as their branded counterpart, Copaxone (Teva).

**HEADACHE & MIGRAINE**

**NOTABLE DEVELOPMENTS IN 2017**

**Phase 3 Findings Signal the Impending Arrival of Monoclonal Antibodies**

Monoclonal antibodies for migraine treatment have been in development for many years and now appear on the verge of approval. Positive findings from pivotal Phase 3 studies for multiple agents suggest that a new class of CGRP inhibitors is set to alter the migraine treatment landscape.

In the EVOLVE-1 study, patients with episodic migraine treated with galcanezumab (Eli Lilly) 120mg over a six-month period experienced an average reduction of 4.7 monthly migraine days, while patients receiving 240mg experienced an average reduction of 4.6 days, compared to an average reduction of 2.8 days for placebo.

In the HALO study, patients treated with fremanezumab (Teva) experienced statistically significant reductions in the number of monthly headache days of at least moderate severity versus placebo (-2.5 days) during the 12-week period after first dose, for both monthly (-4.6 days) and quarterly (-4.3 days) dosing regimens.

In a Phase 2 study, among patients who had been experiencing 15 or more migraine days per month, treatment with erenumab (Amgen) reduced monthly migraine days by 6.6, as compared to a 3.5-day reduction for placebo.

In the May edition of *Practical Neurology* magazine, Peter McAllister, MD, Medical Director of the New England Institute for Neurology and Headache in Stamford, CT, noted that monoclonal antibodies offer several key advantages over traditional small molecule compounds, including “exquisite ‘lock-and-key’ target specificity, long half-life (generally weeks to months), low risk of drug-drug interactions, and limited potential for off-site toxicity,” he wrote.
Neurostimulation Landscape Gains New Player, More Prominence

Despite not receiving the attention of monoclonal antibodies and other therapeutic interventions for migraine and headache, noninvasive neurostimulation continues to stand out as a low-risk alternative or complement to traditional therapies. In April, the has released the use of gammaCore (Electrocore), a noninvasive vagus nerve stimulator for the acute treatment of pain associated with episodic cluster headache in adult patients. The gammaCore device transmits a mild electrical stimulation to the vagus nerve through the skin, resulting in a reduction of pain.

Other devices on the market include the transcutaneous supraorbital neurostimulator (Cefaly) and a single-pulse transcranial magnetic stimulator known as SpringTMS (eNeura). This year, Cefaly released an updated version of its device called the Cefaly II.

ON THE HORIZON

The migraine treatment landscape is poised for major reshaping in 2018, led by the expected arrival of CGRP monoclonal antibodies. "If approved, CGRP monoclonal antibodies would represent a paradigm shift in headache medicine: the first time a class of drugs was commercialized specifically for primary headache prevention, rather than serendipitously discovered after approval for another indication," wrote Dr. McAllister in his May 2017 article. "It is imperative that neurologists develop a working understanding of, and a comfort level with, both monoclonal antibodies and CGRP in the context of treating their headache patients."

The continued growth of noninvasive neuromodulation for headache suggests that awareness of this developing frontier is increasing. According to Stewart J. Tepper, MD, Professor of Neurology at Dartmouth-Hitchcock University, physicians should pay close attention. "If the efficacy of these devices is corroborated, and adverse events remain as negligible as so far they appear to be, their impact could be massive," wrote Dr. Tepper in the May edition of Practical Neurology®.

STROKE

NOTABLE DEVELOPMENTS IN 2017

Window Widens for Endovascular Intervention

Results from the DAWN trial confirmed that the window for reducing disability and improving functional independence in patients with stroke receiving endovascular treatment could extend as far as 24 hours. Specifically, results showed that treatment with the Trevo Retriever (Stryker) significantly improved functional independence at 90 days when compared to medical management alone (48.6% versus 13.1%), a relative reduction in disability of 73 percent. Additionally, one in 2.8 patients treated with the Trevo Retriever within 24 hours of a stroke was saved from severe disability.

In an interview published in the May edition of Practical Neurology® magazine, Tudor G. Jovin, MD, Associate Professor of Neurology and Neurosurgery at the University of Pittsburgh and co-lead investigator of the DAWN trial, noted that these findings suggest the possibility of broadening the current guideline of delivering thrombectomy treatment in a less-than-six-hour timeframe. "We have been using rigid time windows for the selection of patients ever since we started using reperfusion therapy," said Dr. Jovin. "This is the first randomized trial that dispels the notion that treatment beyond this window would not be beneficial."

PFO Closure Reduces Risk of Recurrent Stroke

New studies showed that closing a patent foramen ovale (PFO) significantly reduces the rate of recurrent stroke compared with medical therapy in patients who experienced a cryptogenic stroke and had a PFO.5-7 In the RESPECT study, the Amplatzer PFO Occluder (St. Jude Medical/Abbott Laboratories) was associated with a 45% reduction in the risk of ischemic stroke and a 62% reduction in the rate of cryptogenic stroke.5 The REDUCE trial showed that patients undergoing PFO closure with Cardioform Septal Occluders (WL Gore and Associates) plus antiplatelet therapy experienced a significantly lower incidence of new brain infarctions as compared to patients receiving antiplatelet therapy only.6

ON THE HORIZON

Despite the positive findings for endovascular intervention, optimizing systems of care to implement these treatments on a broader scale remains a work in progress, according to Dr. Jovin. "Right now, the infrastructure lags behind the data; nevertheless, the creation of adequate infrastructure has been identified as a top priority for the field of endovascular treatment of stroke."

For more updates and the latest developments in stroke, read the upcoming January 2018 special comprehensive stroke edition of Practical Neurology®.

Trends That Will Shape the Future of Neurology

A number of developments outside the field may have a significant impact on the management and prevention of neurological disease, as well as patient care. Ahead, Practical Neurology® magazine editorial board members share impressions on how these evolving trends will affect physicians, patients, and the broader discipline.

Red Tape, Rising Costs, and Other Challenges

Neurologists of all backgrounds will likely continue to face a host of challenges in 2018, potentially causing already high burnout rates to continue rising. “Our biggest problem in medicine and especially neurology is the more limited time we spend with our patients,” says Ronald Devere, MD, who cites the requirement of electronic medical records, reduced reimbursement, and rising practice expenses as primary culprits. Additionally, new payment models and increased documentation will significantly affect the amount of time physicians spend with their patients, according to Francis X. Conidi, DO. “As a solo neurologist, I find it harder each year to practice from a reimbursement perspective, added paperwork, and continued intrusion by insurance companies into the doctor-patient relationship.” On the other side of the spectrum, Michael Sperling, MD notes that neurologists practicing in large systems or hospitals “will likely be subject to greater performance pressures in hospitals that are struggling to adapt to changes in financial reimbursement and utilization of facilities.”

Another roadblock to the optimal delivery of care that will become more pronounced over the next several years is the uneven distribution of neurologists, according to Dr. Shannon. Specifically, she says, “the population is aging, and the number of neurologists is not expected to keep pace.” Moreover, Dr. Shannon observes, the increasing prices of new drugs is unsustainable: “Neurological diseases are rare, and each novel approved drug comes with an astronomical price tag. It is critical that we find cost-effective ways to treat our patients.”

Finally, uncertainties in the regulation of the health care system created disturbances in the delivery of services and difficulties in planning for the future, according to Dr. Shaibani. “Until policymakers take serious steps to envision and enact a system that serves the majority, ill-devised policies will continue to restrict medical services,” he observes.

The Expanding Influence of Technology and “Big Data”

The field of neurology will increasingly progress from treatment of symptomatic disease to risk management and disease prevention. According to Jeffrey Cummings, MD, technology will play a critical role in that transition. “Genomic profiles, imaging, blood-based biomarkers, computerized assessments, and personal devices will provide data on disease vulnerability and progression,” he says.

Additionally, the use of telemedicine will continue to expand in 2018 and years to come. “A larger percentage of visits will be virtual and conducted through the computer of the doctor or nurse, with fewer visits to the clinic for face-to-face care,” explains Dr. Cummings.

Advances from the realm of Big Data are also expected to proliferate in 2018, according to Logan Schneider, MD. “Certain groups are capitalizing upon this by establishing data quality and interoperability standards, integrating/linking information across platforms, and devising new sensors to track human health on a more continuous basis,” says Dr. Schneider. “From a neurology perspective, such monitoring can effectively track therapeutic effect and disease trajectories and divergence, in addition to providing a subtle/passive preventive screening process and insights into the true nature and course of disease,” he explains.

A Field Rich With Potential

Despite frustrations due to mounting red tape, as well as unease with changing systems, there is reason to be hopeful that innovations in the understanding of neurological disease will pave a better future for care. “Neurology continues to show great promise,” says Dr. Shannon, due to a combination of increasing understanding of disease, novel approaches to therapy, and the use of technology to better serve patient populations. Additionally, Dr. Sperling notes that many illnesses presently thought to have dismal prognoses will be more effectively treated and managed. “Implementation of better defined diagnostic and treatment pathways and a greater standardization of care will be required to deliver these therapies in an efficient and effective manner.”

Although there is still much to discover about the brain and how it works, Dr. Schneider believes that the field is “primed for groundbreaking discoveries, allowing a new potential for prevention as well as reversal/regeneration.”