Expanding the Scope of Neurology: An Interview with Ralph L. Sacco, MD

New AAN President sees collaboration and wellness as integral to the future of the specialty.

When Ralph L. Sacco, MD, MS, FAHA, FAAN, assumed his role as President of the American Academy of Neurology (AAN) at the recent AAN Annual Meeting in Boston, he had both a clear vision for the future of neurology and a plan for how to get there. “It’s all about teamwork and collaboration across organizations and national boundaries, as well as bringing many constituencies and subspecialties of neurology together,” said Dr. Sacco in an interview with Practical Neurology® magazine. As the first neurologist to serve as president of the American Heart Association (from 2010 to 2011), Dr. Sacco knows something about the importance collaborative and multidisciplinary care, and he is making it a focus of his platform as incoming AAN President: “To provide state of the art care of complex neurological patients, we have to work in teams. Providing integrated and multidisciplinary care requires neurologists to work with a number of different specialists, including rehab physicians, neuropsychologists, neurosurgeons, and multiple professional groups.”

According to Dr. Sacco, this collaborative mindset should extend beyond clinical care and also encompass organizational aspects of the specialty. “The AAN is the largest professional society for neurologists in the world, and we are trying to work across specialties and constituencies to both coordinate and collaborate with the multiple voices of neurology.” That means expanding the reach of the Academy to more fully engage international collaborators, patient-centered organizations, and particularly advance practice providers, he observed. “Advance practice providers are growing fast in our organization, and we want to make sure we can engage them fully in our multidisciplinary team care required for neurological patients,” he said.

Another point of emphasis in Dr. Sacco’s tenure will be personal and professional wellness. One of the most significant challenges facing neurologists and the specialty as a whole is burnout, according to Dr. Sacco. “One of the biggest drivers of burnout is regulatory burden that doesn’t have specific value to the care of patients. Our last President, Dr. Terrence L. Cascino had created a task force to address burnout among neurologists,” he noted. “We are continuing that task force activity and turning it into a wellness task force to begin to think about ways to mitigate and reduce burnout and improve the lives of our neurology members.”

At the last two AAN Annual Meetings, many features have been added to modernize educational formats, said Dr. Sacco. Among these is a collection of wellness programs directed at individual members to enhance resilience, such as yoga and tips for handling stress. The AAN has also created more experiential learning sessions, including “Ask the Expert” panels, difficult cases, and special debate formats. “We’ve incorporated a lot of different approaches to bring education to our members in a more contemporary fashion for both individual and educational enrichment,” Dr. Sacco explained.

The AAN is also addressing wellness and burnout through their Government Relationships Committee to coordinate with CMS and federal regulators in an effort to improve the practice of neurology and reduce regulatory hassle. Telemedicine is also a major part of this platform. “We’re trying to expand access through better reimbursements for telemedicine, which will improve our ability to care for the growing number of patients with neurological conditions,” according to Dr. Sacco.

Another challenge facing the specialty that Dr. Sacco intends to address in his tenure is the workforce shortage. Roughly 2.6 percent of US medical students choose neurology as a profession, which has remained stable for too long, according to Dr. Sacco. “To meet the demand for neurological care by an aging population, we are actively working on programs to stimulate more students to get excited about careers in neurology,” he says.

Dr. Sacco is hopeful that the Academy’s strategies to improve wellness and collaboration at various levels will expand the scope of neurology practice and encourage greater participation in the field. “Neurology needs to be thought of as interventional, preventive, and also as a regenerative specialty. If we can get more people thinking about how we can cure, treat, prevent, and hopefully even regenerate neurological conditions, in the future we can also get more medical students interested in our profession,” he noted. “We’ve made a lot of strides, and the research discoveries in the last few years are putting us at a great point to bring some of these strides much more into the clinic.”
MS Topography App Launches

A new app launched at the AAN Meeting offers a visual way of understanding multiple sclerosis (MS). The app is a disease simulation that visualizes MS as a swimming pool. According to creator and MS specialist Stephen C. Krieger, MD, the app depicts an MS disease topography, mapped in the central nervous stem, as a tool to better understand the variable way MS can develop and change over time. “We have categories of MS clinical course—relapsing-remitting disease, primary progressive, secondary progressive—that clinical trials are based on, but in practice we often see a mixture of relapsing and progressive disease, and so I’ve tried to conceptualize that as a continuum,” said Dr. Krieger in an interview. Thus, the app can serve as a tool for helping patients and physicians better understand the disease and its progression. “People learn through metaphor. They learn from tying something they don’t understand through something that they do.”

Dr. Krieger noted that progression is the loss of reserve and the ability to compensate for damage. “More of underlying becomes clinically revealed and people have progression of multifocal signs and symptoms of MS. I call that the recapitulation hypothesis,” he noted. Dr. Krieger presented poster data at the AAN meeting evaluating the recapitulation hypothesis using a longitudinal clinical cohort (P4.392). The pilot empirical test examined a subgroup of 10 patients who transitioned from relapsing MS to secondary progressive MS. Results indicated that roughly 83 percent of prior acute relapse symptoms were noted at the transition to secondary primary MS and roughly 91 percent of symptoms were present at most recent visit. According to Dr. Krieger, these data support the recapitulation hypothesis and the model’s depiction of disease topography as the loci of subsequent clinical progression.

In terms of next steps, Dr. Krieger believes that the poster lays out a methodology that could be studied with big cohorts to refine the model and ultimately use it in a more personalized way. “The potential of this model to encapsulate certain key features of the disease that we haven’t necessarily put all together before, and if hypothesis it proves to be true, would have real implications for how we as clinicians look at patients with this disease.”
Greenwich Pharmaceuticals Reveals Next Steps in the Pipeline for Epidiolex

GW Pharmaceuticals presented positive results from a second Phase 3 study (GWPCARE3) of Epidiolex (cannabidiol or CBD) in children and adults with Lennox-Gastaut syndrome (LGS). In the GWPCARE3 study, adding Epidiolex to patients’ current treatment significantly reduced the frequency of drop seizures at both the 10 mg/kg/day and 20mg/kg/day doses. During the 14-week treatment period, patients taking both doses of Epidiolex saw a significantly greater median reduction in monthly drop seizures (37 percent and 42 percent, respectively) compared with a 17 percent reduction for placebo. In addition, 66 percent of patients/caregivers with Epidiolex 10mg/kg/day and 56 percent in the Epidiolex 20mg/kg/day group reported an improvement in overall condition, compared to 44 percent for placebo based on the Subject/Caregiver Global Impression of Change (S/CGIC) questionnaire. Epidiolex was also generally well tolerated in the trial. The pattern of adverse events was consistent with previously reported Phase 3 studies.

According to lead investigator Anup Patel, MD, Epidiolex potentially will give physicians a new option to treat populations that tend to be very vulnerable. “In epilepsy we’re used to looking at new molecules and mechanisms of action. We’re dealing with a population that’s very desperate and in need of new treatments,” said Dr. Patel in an interview. “CBD represents a new mechanism, so if patients have previously failed medicines that work differently they can try a new way of attacking the same problem and hopefully get better success.”

According to Greenwich Pharmaceuticals CEO Justin Gover, the company has taken the right steps in the development of a novel agent such as CBD. “This is a development program where 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 FDA and provide meaningful important therapy to patients,” said Mr. Gover in an interview. “Our job now as a company is to do the right thing by the product, make sure that we present a compelling case to FDA, and have a team that can launch this and manufacture it appropriately.”

Findings Support Perampanel in Pediatric Patients with Generalized Tonic-Clonic Seizures

Eisai presented a meta-analysis of published clinical trials that supports the extrapolation of anti-epileptic drug efficacy data from adult to pediatric patients (ages four and older) living with primary generalized tonic-clonic (PGTC) seizures. The study, which was chosen as part of the “Best Of” epilepsy panel presentation, showed that the mean difference in median percent reduction of PGTC seizure frequency and the estimated risk ratios of 50 percent responder rate were not age-dependent. Included in the meta-analysis were the results from a global Phase 3 clinical trial of perampanel (Fycompa) administered as an adjunctive therapy.
Endovascular Care Delivery: Racial and Regional Disparities Abound

Access to endovascular care is significantly impacted by factors such as race, region, and hospital, according to findings presented at the AAN meeting and published in the April 18 edition of Neurology. Investigators analyzed data from a large registry to determine use of endovascular therapy in ischemic stroke patients.

Among more than 58,000 patients in Florida and Puerto Rico, 3.6 percent received thrombectomy. Compared to those patients not treated with endovascular therapy, patients treated with endovascular thrombectomy had a lower risk of vascular risk factors, more severe strokes, arrived earlier via EMS (often during work hours), and were often treated in large hospitals in South Florida. In light of these disparities based on region, race, and other factors, the authors recommended efforts to improve access to endovascular treatment to all eligible patients.

Parkinson’s Disease May Originate in the Gut

Parkinson’s disease may start in the gut and spread to the brain via the vagus nerve, according to a study published in the April 26, 2017 edition of Neurology. When researchers analyzed the results from preliminary research for the two different types of vagotomy surgery, they found that people who had a truncal vagotomy at least five years earlier were less likely to develop Parkinson’s disease than those who had not had the surgery and had been followed for at least five years.

A total of 19 people who had truncal vagotomy at least five years before developed the disease, compared to 3,932 people who had no surgery and had been followed for at least five years. By contrast, 60 people who had selective vagotomy five years earlier developed Parkinson’s disease. Researchers found that people who had a truncal vagotomy at least five years before were 40 percent less likely to develop Parkinson’s disease than those who had not.

“Endovascular Care Delivery: Racial and Regional Disparities Abound”

American Academy of Neurology 2017 Annual Meeting Coverage

ON THE CUTTING EDGE OF EPILEPSY

Amy Brooks-Kayal, MD

“It’s a very exciting time for us in epilepsy. We have lots of medications that treat seizures but we don’t have any medications that are truly targeted or disease modifying, or specific to people with different types of epilepsy. There are a lot of new and really exciting therapies that are coming out of preclinical work by our basic and translational scientists that really promise to change the face of how we take care of people with epilepsy in the next decade.”

Amy Brooks-Kayal, MD provided a snapshot of new innovations and developments in epilepsy care. Watch the video at PracticalNeurology.com.
AAN Unveils New Guideline for SUDEP

The American Academy of Neurology and the American Epilepsy Society (AES) have released a new joint guideline for sudden unexpected death in epilepsy (SUDEP). SUDEP is rare in children, affecting just one in 4,500 children every year, while in adults it affects one in 1,000 individuals every year, according to the new study.

Based on a review of all available evidence showing, investigators found that general tonic-clonic seizures represent a major risk factor for SUDEP. The guideline therefore recommends that health professionals tell people with epilepsy that controlling these seizures and seizures in general may reduce the risk of SUDEP.

The new guideline, which was also endorsed by the International Child Neurology Association, was published in the April 24 edition of Neurology.

New Data Reinforce Efficacy of Ocrelizumab

New data from Genentech show the benefits of Ocrevus (ocrelizumab) in relapsing multiple sclerosis (MS). In a pooled analysis of Phase 3 OPERA studies, ocrelizumab reduced the relapse rate by 55 percent compared to interferon beta-1a. Additional analyses of the OPERA studies showed the efficacy of ocrelizumab in people with early relapsing MS, suppressing more than 90 percent of active MRI lesions over two years compared with interferon beta-1a in these patients. In the same early RMS patients, ocrelizumab also increased the proportion those who achieved No Evidence of Disease Activity (NEDA) by 76 percent compared with interferon beta-1a over two years.

In an analysis of pooled data from the Phase 3 relapsing MS open-label extension (OLE) studies, patients who switched from interferon beta-1a to ocrelizumab experienced reductions in relapse rates and MRI brain lesions. Moreover, patients who were treated with ocrelizumab from the start showed a sustained benefit at three years.

Sunovion Investigates Potential of Aptiom for Seizure Improvement

Sunovion Pharmaceuticals presented eight posters supporting the use of Aptiom (eslicarbazepine acetate) to treat partial-onset seizures (POS). More specifically, the posters included data that support the use of Aptiom as monotherapy in adults with refractory POS. According to David Blum, Global Head of Neurology Clinical Research at Sunovion Pharmaceuticals Inc, the data reviewed special situations as well as safety issues, in effort to help guide practitioners so that they can provide the best care.

In one study evaluating categories of seizure improvement, Dr. Blum noted that instead of looking just at how many patients get worse, they analyzed how many patients improved. “We found that about 10 percent of patients in the program became seizure free, and these are patients who are not controlled with prior AEDs,” says Dr. Blum in an interview.

The company also presented analyses supporting a supplemental new drug application (sNDA) for the use of Aptiom in children four years of age and older.
Long-Term Data Supports Brain Responsive Neuromodulation for Reduction of Seizures

Two new studies offer long-term perspective on the efficacy and safety of brain responsive neuromodulation for the reduction of seizures. One study evaluated the effects of NeuroPace's RNS System in patients with medically intractable mesial temporal lobe epilepsy (Epilepsia. 2017 Apr 11), while the other looked at its effects on patients with medically intractable seizures arising from eloquent and other neocortical areas (Epilepsia. 2017 Apr 7). In the latter study, the median reduction in seizure frequency was 51 percent to 70 percent at six years. Moreover, 26 percent of patients experienced at least one seizure-free period at six month or longer, and 14 percent experienced at least one seizure-free period of one year or longer.

"These studies suggest that the RNS device is a significant addition in the treatment of epilepsy for patients who did not have a surgical option previously," said lead author Barbara C. Jobst, MD in an interview. While patients are generally under-referred for surgical treatment, a significant portion of these patients is not eligible for surgery, Dr. Jobst noted. "For many patients there are limitations for surgery, such as those who would have deficit if we removed the seizure focus, or others who have more than one seizure focus or who may have significant memory deficit." In these patients, the RNS device may be particularly beneficial. "You can implant the device in seizure onset zones, even if there are more than one. You can also implant it in areas that in the past we would have considered 'eloquent' areas of the brain." These include areas that control language and motor skills, which Dr. Jobst noted would not be interrupted by the device.

According to Dr. Jobst, the RNS device is another valuable treatment tool in high-level epilepsy care that heightens the profile of surgical epilepsy care. She further observed that many patients are still not receiving the advanced treatment they may require. "A lot of patients on medications continue to have seizures and don't get sent to comprehensive epilepsy center; this is a problem that has plagued our community for a long time." Nevertheless, she is hopeful that continued awareness for devices such as RNS and a growing platform of surgical interventions will compel physicians to make the appropriate referrals. "The goal is 100 percent seizure freedom," said Dr. Jobst. "If someone has intractable epilepsy, consider a referral to a comprehensive epilepsy center for surgical evaluation."

Stroke Hospitalization Rates and Risk Factors Increasing in Young Adults

Rates of acute ischemic stroke are increasing in young adults, new findings suggest (JAMA Neurology, April 10). Investigators analyzed stroke hospitalization rates as well as associated risk factors among patients between the ages of 18 and 64 years of age. They found that acute ischemic stroke hospitalization rates increased significantly for both men and women. Moreover, since 1995-1996, rates have almost doubled for men between 18 and 44 years of age, while rates for men and women aged 55 to 64 have not changed from 2003-2004. They also found that prevalence of stroke risk factors—such as hypertension, lipid disorders, diabetes, tobacco use, and obesity—among those hospitalized for acute ischemic stroke continued to increase from 2003-2004 through 2011-2012 for both men and women aged 18 to 64 years.

The investigators concluded that these findings highlight the importance of emphasizing stroke prevention and overall health in younger adults. "Preventing and controlling stroke risk factors among young working-age adults can save lives, reduce disability, decrease societal health care costs, and improve the quality of life for hundreds of thousands of Americans and their families," the authors wrote.
FDA Greenlights First New Treatment for ALS in More Than Two Decades

The FDA has approved Radicava (edaravone, MT Pharma), as an intravenous infusion treatment for amyotrophic lateral sclerosis (ALS). Radicava is the first treatment approved for the treatment of ALS in 22 years. The approval followed a 13-year comprehensive clinical development program, in which a pivotal Phase 3 study (MCI186-19) evaluating 137 people with ALS demonstrated that patients who received Radicava for six months experienced roughly 33 percent less decline in physical function than those receiving placebo.

The most common adverse reactions that occurred in more than 10 percent of patients were bruising, gait disturbance, and headache.

Radicava is administered in 28-day cycles by intravenous infusion. It takes 60 minutes to receive each 60 mg dose, according to the company. For the initial cycle, the treatment is infused daily for 14 consecutive days, followed by a two-week drug-free period. All cycles thereafter are infused daily for 10 days within a 14-day period, followed by a two-week drug-free period.

The cost of Radicava per year is roughly $145,000. To bolster access to the drug, MT Pharma has created the Searchlight Support program, which offers personal case management, reimbursement support, and 24/7 clinical support to patients.

First Treatment for Tardive Dyskinesia Approved in US

The FDA approved the selective VMAT2 inhibitor Ingrezza (valbenazine, Neurocrine Biosciences), making it the first treatment approved in the US to treat adults with tardive dyskinesia. The efficacy of Ingrezza was shown in a clinical trial of 234 participants that compared Ingrezza to placebo. After six weeks, participants who received Ingrezza had improvement in the severity of abnormal involuntary movements compared to those who received placebo. Adverse events of Ingrezza include sleepiness and heart rhythm problems. Its use should be avoided in patients with congenital long QT syndrome or with abnormal heartbeats associated with a prolonged QT interval.

Tardive dyskinesia is sometimes seen in patients who have been treated with antipsychotic medications for long periods to treat chronic conditions, such as schizophrenia and bipolar disorder. It can also occur in patients taking antipsychotic medications for depression and certain medications for gastrointestinal disorders and other conditions.

According to Chris O’Brien, Chief Medical Officer of Neurocrine, this approval is significant because it addresses significant unmet need in patients suffering from TD. “For the roughly five to eight percent of patients who were successfully dealing with their mental illness, tardive dyskinesia makes it so difficult for these patients,” said Mr. O’Brien in an interview. With the new approval, Mr. O’Brien noted, patients can “re-emerge again and get their lives back.”

Regarding the drug itself, Mr. O’Brien noted that the labeling makes clear that the FDA recognized the benefit of the drug. “The label is a very straightforward and leaves nothing to the imagination for the prescribing physicians,” he said. “It makes the drug available to all TD patients, with no limitations on severity and no requirement for the doctor to utilize AIM scores to justify the patients being prescribed the drug.”

New Therapy for Chorea Associated with Huntington’s Disease Wins Approval

The FDA approved Austedo (deutetrabenazine, Teva Pharmaceuticals) tablets for the treatment of chorea associated with Huntington’s disease (HD), making it just the second product approved for the disease. The approval was based on results from a phase 3 randomized, placebo-controlled study to assess the safety and efficacy of Austedo in reducing chorea in patients with HD (First-HD). In 90 ambulatory patients with manifest chorea associated with Huntington’s disease, Total Maximal Chorea Scores for patients receiving Austedo improved by approximately 4.4 units from baseline to the maintenance period (average of Week 9 and Week 12), compared to approximately 1.9 units in the placebo group. The treatment effect of -2.5 units was statistically significant. The Maintenance Endpoint is the mean of the Total Maximal Chorea Scores for the Week 9 and Week 12 visits. One week after discontinuation of the study medication, the Total Maximal Chorea Scores of patients who had received Austedo returned to baseline.

Previously referred to by the developmental name SD-809, Austedo is the first deuterated product to earn FDA approval.