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New Treatment Guidelines for Acute Ischemic Stroke Open the "Golden Window" for Treatment to 6-24 Hours

On January 24, 2018, the American Heart Association (AHA) and the American Stroke Association announced new evidence-based guidelines for treatment of adults with acute ischemic stroke (AIS) (Stroke. published online January 24, 2018) replacing previous guidelines published in 2013 (Stroke. 2013;44:870–947). The new guidelines are endorsed by the American Association of Neurologic Surgeons, the Congress of Neurologic Surgeons, and the Society of Academic Emergency Physicians.

Prehospital-, urgent-, and emergent-treatment are addressed and include intravenous and intra-arterial therapy and in-hospital management, including secondary stroke prevention measures in the first 2 weeks poststroke. Implementation of regional stroke systems is supported.

The following strong recommendations with level A evidence are new: development of regional stroke care systems, quality improvement projects for emergency department personnel and multidisciplinary teams to increase safety of IV thrombolytic treatment, use of teleradiology for rapid diagnosis, and participation in stroke-data repositories. Mechanical thrombectomy with the goal of reperfusion is recommended for patients who meet specific criteria and can be initiated within 6-24 hours of symptom onset.

In addition it is recommended that multimodal CT and MRI, including after perfusion imaging should not delay administration of IV alteplase, the CT hyperdense sign should not be used as a criterion for withholding alteplase therapy, and sonothrombosis should not be used as adjuvent therapy with IV alteplase.

Although most new evidence for the guidelines was previously incorporated into focused updates, scientific statements, and published guidelines by the AHA, these new guidelines are comprehensive and updated.

Simultaneously, the AHA published articles by Smith et al. on accuracy in diagnosing large vessel occlusion in adults with suspected stroke, a systematic review for the early management of adults with AIS (Stroke. published online January 24, 2018.), and on the effect of dysphagia screening strategies on outcomes for patients after AIS (Stroke. published online January 24, 2018.).

The American College of Cardiology/AHA class of recommendations are given for each recommendation in a collection of tables that also summarize the evidence for new or revised guidelines. Unchanged guidelines are included for comprehensiveness, though without the evidence included, unless new evidence is available.

FDA Grants Approval for Senza II Spinal Cord Stimulation System Delivering HF10 Therapy

On January 8, 2018, Nevro Corporation, a global medical device company, announced that it has received approval from the Food and Drug Administration (FDA) for its next-generation Senza II Spinal Cord Stimulation (SCS) System delivering high-frequency (HF10) spinal cord stimulation (SCS) at 10,000 Hz. Traditional SCS delivers electrical pulses at less than 1,200 Hz and usually between 40-60 Hz, creating paresthesia that is thought to "mask" the patient's sensation of pain. In contrast, HF10 SCS does not cause paresthesia and has earlier onset of analgesic effects.

Nevro's Senza II system offers HF10 therapy with a smaller implantable pulse generator that is as effective and durable as their previous system. The Senza II system delivers Nevro's proprietary HF10 SCS therapy via small electrodes on leads placed near the spinal cord and connected to a compact, battery-powered generator implanted under the skin. HF10 SCS therapy is the only SCS to date that has been shown superior to traditional SCS for back and leg pain in a comparative study.

Dr. Tom Simopoulos, Director of Pain Medicine and Co-Director of the Spine Center at the Beth Israel Deaconess Medical Center in Boston, MA said, "The reduced size and optimized design of the Senza II IPG allow for greater patient comfort and placement options. . . . it delivers HF10 therapy, a non-opioid treatment option that provides profound and paresthesia-free pain relief for patients."

Parkinson's Outcomes Project Enrolls 10,000th Patient and Releases Key Findings

The Parkinson's Outcomes Project, launched in 2009 as a small pilot and funded by the Parkinson's Foundation, announced a major milestone goal on January 10th, 2018, with the enrollment of its 10,000th patient. This clinical study, the largest of Parkinson's disease (PD) to date, has grown to international scope and includes 29 expert clinics and investigators in the United States, the Netherlands, Canada, and Israel. Over 25,000 clinical visits and information from almost 9,000 family-care partners are incorporated. The study includes both newly diagnosed patients and those with chronic illness, regardless of age at diagnosis. Over 100 participants have lived with PD for more than 30 years, and 83 participants were diagnosed prior to age 30.

The Parkinson's Outcomes Project evaluates a broad range of factors that affect patients with PD, including the benefits and efficacy of medications and therapy, motor symptoms, cognitive effects, best candidates for specific treatments, benefits of exercise, caregiver impact, and the role of anxiety and depression.

Peter Schmidt, PhD, Senior Vice President, Chief Research and Clinical Officer of the Parkinson's Foundation, said "Our goal was to understand the impact of Parkinson's on everyone living with the disease . . . (and) represents the broadest and most inclusive patient population ever assembled in a clinical study of Parkinson's. The data we are collecting is informing trials to deliver new and better therapies."

Key findings include the importance of regular care from a neurologist for patients with PD, noting this could be lifesaving for thousands. The importance of mental health care has also been shown, as depression and anxiety are identified by the study as key factors determining the overall health of patients with PD. Exercise as part of the treatment plan is also emphasized, as increasing general movement to 2.5 hours a week or more slows the decline in quality of life.

As reported in *Neurology* last December, the Parkinson's Outcomes Project has also shown that women with PD are at a disadvantage compared to men with PD, because women receive less regular support from caregivers throughout the course of their illness and less caregiving from family versus paid caregivers for everything from daily care to doctor visits (Neurology. 2017 Dec 14. pii: S1353-8020(17)30838-6.) The lead author, Nabila Dahodwala, MD, MS, from the University of Pennsylvania, emphasized the significance of this finding as informal care is a vital component of care for people with PD. Understanding how best to provide day-to-day care can help improve quality of life for patients and their families.

John L. Lehr, Chief Executive Officer of the Parkinson's Foundation, said "The Parkinson's Foundation recently established the Women and PD Initiative to address significant gender differences in the experience of Parkinson's . . . shedding light on and finding solutions for women-specific issues to help improve the health and well-being of women living with Parkinson's.

Guidance for the Use of Opioids in the Treatment of Refractory Restless Leg Syndrome

On January 8, 2018, *Mayo Clinic Proceedings* published an article on appropriate use of opioids for treating refractory restless legs syndrome (RLS) by members of the Scientific and Medical Advisory Board of the Restless Legs Syndrome Foundation (Mayo Clin Proc. 2018;93:59-67.) The article offers guidance for clinicians on the appropriate use of opioids to treat refractory RLS, including monitoring, addiction risk assessment, and safe prescribing practices.

The incidence of RLS is estimated as 2% to 3% percent of adults, and while most find initial relief from nonopioid medications, these can cause serious side effects and lose efficacy over time. In such cases, opioids given at relatively-low–total-daily doses may offer relief for patients that can significantly improve quality of life.

The paper summarizes clinical trials and case series showing efficacy of opioids for treating RLS, and the authors conclude that risk of addiction is relatively low as doses are much lower than that used for chronic pain conditions. They further recommend trying other medications and alternative therapies before prescribing opioids, assessing all patients for risk of addiction, and educating them on responsible use, as well as starting with the lowest possible dose. In addition, they suggest having patients sign an "opioid contract," agreeing not to share opioid medications with others and to having their physician monitor their opioid use over time.

Lead article author Michael Silber MB, ChB said, "The quality of life of patients with severe RLS is very low. They have intense insomnia; they may have suicidal depression. Physicians should make appropriate use of opioids when other treatment options are ineffective. We have published this paper so that both specialists and primary care physicians can feel more comfortable prescribing opioids to RLS patients, not feel that they are at risk as physicians in treating these patients, and help relieve their suffering."

The Food and Drug Administration Mini-Sentinal Shows Rivaroxaban Is Associated with a Lower Risk of Ischemic Stroke Versus Warfarin

Rivaroxaban (Janssen Pharmaceuticals) is an antithrombotic medication that inhibits clotting Factor Xa. It is available in oral tablet formulation for patients at risk of, or being treated for, deep vein thrombosis (DVT) and pulmonary embolism (PE) or to help prevent stroke and blood clots in patients with atrial fibrillation without heart valve disease. Rivaroxaban may reduce the risk of DVT, which can lead to PE in people who are having hip replacement or knee replacement surgery.

The Food and Drug Administration (FDA) Mini-Sentinel assessment confirmed safety and efficacy of rivaroxaban in a phase 3 clinical trial, the results of which were published in *Pharmacoepidemiology & Drug Safety*. The findings are consistent with other analyses. Of note, the FDA Mini-Sentinel report showed a lower risk of ischemic stroke with rivaroxaban compared to warfarin throughout the more than 3-year analysis.

The Mini-Sentinal is a working pilot project to develop active safety surveillance of approved FDA-regulated medical products. It is part of a national electronic system for such monitoring and uses existing electronic healthcare data from multiple sources.

"We're pleased to see the Sentinel Initiative in action and that the FDA's findings are consistent with results from other independent real-world and post-marketing studies," said Paul Burton, MD, PhD, FACC, Vice President, Medical Affairs, Janssen Pharmaceuticals, Inc.

Sublingual Formulation of Riluzole Bioequivalent to Tablet Formulation

On January 9, 2018. Biohaven announced positive results from its bioequivalence study of BHV-0223, an innovative sublingual formulation of riluzole, currently available as a 50-mg tablet, which is currently the standard-of-care treatment for patients with amyotrophic lateral sclerosis (ALS), but can be difficult for patients with ALS to swallow. Topline results in a study with 138 healthy volunteers who were administered 40 mg of BHV-0223 sublingually and 50 mg of riluzole in tablet form under fasted conditions showed area-under-the-curve and peak exposures of approximately 90% and 113%, respectively, compared to those generated by generic riluzole. The 90% confidence intervals were within the 80% to 125% range used to define bioequivalence.

Biohaven is developing BHV-0223 as a potential treatment for patients with ALS and received regulatory feedback from the Food and Drug Administration (FDA) that no additional efficacy or toxicology studies are necessary for submission of a new drug application (NDA) for this indication. Biohaven anticipates completing an NDA submission in the first half of 2018.

While riluzole is FDA-approved for ALS, conventional tablets may be difficult to administer to paatients with ALS, who often have dysphagia. The sublingual BHV-0223 dissolves in seconds and does not require swallowing. In addition, riluzole is associated with dose-dependent effects on liver tests (transaminases), which is significant because BHV-0223 offers bioequivalent exposures with a 20% lower dose. Based on this observation and reduced drug exposure to the liver, BHV-0223 may have a lessened risk for causing liver enzyme elevations.

Vlad Coric, MD, Chief Executive Officer of Biohaven, commented, "Sublingual BHV-0223 is unique in that it is . . . optimized to allow administration to patients with dysphagia and to provide therapeutic blood levels at a lower dose for all patients suffering from ALS."

PROMISE Phase 3 Trial for Chronic Migraine Prevention Meets Primary and All Key Secondary Endpoints; Shows Reduction in Migraine Risk

Alder Biopharmaceutical reported on January 8, 2018 that their injectable calcitonin gene-related peptide (CGRP) inhibitor, in phase 3 clinical trials, reduced monthly migraine days by 50% or more in 3 of 5 patients with migraine treated, and that 33% of patients had a ≥ 75% reduction in headache days per month with a 52% reduction in migraine risk beginning on day 1. Eptinezumab is a monoclonal antibody that targets CGRP. Alder plans to file a biologics license application in the second half of 2018. If approved, eptinezumab will be the first infusion therapy approved for migraine.

As announced in 2017, the first of 2 phase 3 trials, PROMISE 1 and 2, both of which are double-blind, randomized, placebo-controlled studies had shown that eptinezumab significantly reduced the number of migraine days per month versus placebo.

The second phase 3 trial, PROMISE 2 enrolled 1,072 patients who met the International Headache Congress' definition of chronic migraine: 15 or more headache days

per month in which at least 8 headache days include characteristics of migraine. Treatment with eptinezumab reduced the number of headache days from a baseline of 16.1 days per month to 7.9 days per month over the 12-week treatment period versus a reduction to 10.5 days with placebo ($P = .0001$). In addition, 33% of patients had a ≥ 75% reduction in headache days per month compared to 15% for placebo ($P < .0001$). Rapid prevention was also achieved; there was a 52% reduction in migraine risk beginning on day 1 after infusion compared to 27% for placebo ($P < .00011$). Safety and tolerability findings were similar to those in previously reported eptinezumab studies.

"These results represent an important part of the significant step forward that patients who suffer from migraine. . . are about to experience," said Peter Goadsby, MD, PhD DSc, Neurologist and Headache Specialist at the University of California, San Francisco Medical Center, stating that rapid onset of sustainable benefits after 1 administration represented a "paradigm shift" in migraine preventive treatment with the potential for "patients to experience early and meaningful periods of migraine freedom if new treatments become approved."

The Generational Technology Gap May Be Closing—Even in Patients With Dementia

On January 16, 2018, Senior Helpers, a provider of in-home services for seniors who wish to remain in their homes despite age-related illnesses and mobility challenges including dementia, Alzheimer's disease, and Parkinson's disease, shared results of a survey of 1,000 of their clients regarding their attitudes to, and use of, technology.

They found that more than 68% of respondents, who were 65 years of age and older, rated their technology skills average or above average. The survey examined seniors' attitudes on social media, internet use, and phone or tablet applications (apps). Although 71% of survey respondents did not consider themselves "tech-savvy", nearly 60% thought that younger generations underestimated their knowledge and aptitude for technology.

Additional findings include that 39% of seniors use technology to help get things done more efficiently, and 31% embrace it as a matter of "pure survival." A smart phone was the tech innovation that 29% of seniors couldn't live without, and 70% of the seniors used a smart phone versus 13% who still do not own a cell phone. Regarding app usage, 23% use social media apps, 17% use maps and navigation, 14% use online banking, and 8% use games.

As medicine continues to make use of digital technology from the electronic health record to text-messaging, it is important for all physicians to understand their patients' facility with technology. Especially for neurologists, it is notable that seniors with neurologic conditions of dementia, Alzheimer's disease, and Parkinson's disease can use digital technology.

Peter Ross, CEO and cofounder of Senior Helpers said, "Technology is constantly evolving, but seniors are much more adept at using tech than many people give them credit for; it's become integral to so many other aspects of their lives, they are embracing it."

Parkinson's Advocates in Research Leadership Awards

On November 29th, 2017, The Parkinson's Foundation announced $60,000 in support of patient-scientist teams to develop innovations to engage patients in their own care. These awards expand Parkinson's Advocates in Research (PAIR), a program pioneered by the Parkinson's Foundation to advance researcher–patient collaboration and patient-centered research. The PAIR program highlights the Parkinson's Foundation's commitment to ensuring that research is targeted toward meeting patients' current needs as well as improving treatment and finding cures.

Awards are available for up to $10,000 for patient-centered research projects. This year's awards include virtual case managers, mindfulness-based stress reduction programs, collaboration between neurology and psychiatry, engagment of patients from underserved communities in research, use of digital wearables to track exercise, and gait assessment with video game systems.

Research advocates in the program all live with Parkinson's disease (PD) or are caregivers for someone with PD. All have received training through the PAIR program to understand how to advocate for PD research. PAIR advocates educate their communities, sit on Food and Drug Administration committees, and serve on study steering committees. Together they have worked with over 400 researchers to influence stakeholders and inform research.

The Parkinson's Foundation partners with Centers of Excellence, 42 medical centers that deliver care to more than 100,000 people with PD every year, to determine why certain teams achieve the best outcomes. Each center must meet rigorous criteria in the areas of clinical care, patient service, professional education, and research.

Fernando Cubillos, MD, who provides operations oversight for the Parkinson's Outcomes Project, has said, "Our

goal is to help identify the best care and disseminate that information widely."

This year's awardees include Madeleine Hackney, PhD, from Emory University School of Medicine, and Ron Wincek, a PAIR advocate who lives with PD. Their project seeks to engage underserved older adults with PD to engage in and help recruit others to research studies.

Dr. Hackney said "Our team has found that patients have valuable and often surprising insights that can improve our work in research, care, and support. I applaud the Parkinson's Foundation for investing in our efforts to encourage research participation in underserved communities."

Applications Being Accepted for the Science and PINS $25, 000 Prize for Neuromodulation

The American Association for the Advancement of Science (AAAS), publisher of the journal *Science,* announced on January 23, 2018, that they are accepting applications for the Science and PINS Prize for Neuromodulation. This is a highly competitive prize that honors scientists making contributions to research in neuromodulation, defined as "any alteration of nerve activity through delivery of physical (electrical, magnetic, optical) stimulation to targeted sites of the nervous system." The prize was established in 2016 and is awarded for outstanding research in the field of neuromodulation as described in a 1,500-word essay submitted to the prize committee. The winner is awarded $25,000, travel to an awards ceremony, and publication of their essay in *Science*.

Entrants must be junior investigators who earned an advanced degree within the last 10 years and were 45-years old or younger as of January 1, 2018. Their essay must describe research they have directed or carried out themselves over the last 3 years and the implications of that research on neuromodulation. The deadline for submission is March 15, 2018, and the rules for entry can be found at http://www.sciencemag.org/prizes/pins/rules.

The AAAS was founded in 1848 and includes over 254 affiliated societies and academies of science. Their flagship publication, *Science*, was founded by Thomas Edison and has the largest paid circulation of any peer-reviewed general scientific journal in the world.

Beijing PINS Medical Equipment Co. Ltd., is a high-tech enterprise with a focus on neuromodulation. The clinical products they have developed to date include deep brain and vagal, spinal, and sacral nerve stimulators. The company name is derived from a Chinese word meaning "Magic Pin."

First Prospective Registry Shows Efficacy of Neuromodulation of the Sphenopalatine Ganglion for Treating Cluster Headache

On January 25, 2018, *The Journal of Headache and Pain* published 1-year results from an open-label registry trial, Pathway R-1, evaluating the efficacy of sphenopalatine-ganglion stimulation (SPGs) (Pulsante, Autonomic Technologies) for the treatment of both chronic and episodic cluster headache.

Over a full 12 months, 85 patients with cluster headache (78 chronic and 7 episodic) were followed, and 68% of patients had a significant reduction in the frequency of cluster-headache attacks and/or achieved pain relief in most cluster-headache attacks. Patients experienced, on average, 42.9% fewer cluster headaches at 12 months ($P < .0001$, n = 85) than their baseline number of attacks before starting SPGs. This reduction was seen mostly in the first few months and was sustained through the full year. Patients also reported improvement in quality of life, reduced disability, and less medication use. Altogether, these patients used SPGs to treat 13,600 cluster headache attacks acutely.

As described in this issue of *Practical Neurology* by Tepper and Tepper (p. 42), SPGs stimulates the sphenopalatine ganglion (SPG), a nerve bundle behind the nose. The Pulsante SPG microstimulator is a miniaturized wireless device implanted above the upper jaw. Patients control the stimulator with an external remote control that they hold next to their cheek to provide on-demand therapy of acute headache attacks. Upon pain relief, the patient moves the controller away from their cheek to stop therapy. Implantation is done in an oral procedure of 60 to 90 minutes, which leaves no visible scar. Therapy is customized for each patient during follow up visits.

Patients experienced mild to moderate side effects similar to those seen in the Pathway CH-1 trial, which generally resolved within a few months. Side effects were similar to those of other orofacial procedures. Overall patient satisfaction was high with 86% of patients in the study stating they would recommend SPGs to others with cluster headache.

"This study's results are very encouraging because they reinforce clinical results seen in earlier cluster headache studies with SPG stimulation and demonstrate the therapy's effectiveness in patients suffering from the burden and pain of cluster attacks," said Niamh Pellegrini, President and CEO of Autonomic Technologies. ■