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NEUROLOGY REVIEWS®

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Most eligible stroke patients in the U.S. now get tPA within an hour

HONOLULU—The speed at which eligible U.S. patients with acute ischemic stroke receive thrombolytic therapy has surged in recent years, and by the third quarter of 2018, a nationwide U.S. program aimed at boosting the number of stroke patients who receive thrombolysis in a timely way met its most recent speed targets.

By the second half of last year, 75% of acute ischemic stroke patients treated at any of the 913 U.S. hospitals in the Get With the Guidelines-Stroke program received intravenous tissue plasminogen activator (tPA; alteplase) within 60 minutes of their hospital arrival (their door-to-needle time [DTN]), and 52% received tPA with a DTN time of 45 minutes or less. These levels met the treatment-speed goals set by the second phase of the Target: Stroke program, which called for delivering tPA to 75% of appropriate stroke patients within a DTN time of 60 minutes, and within 45 minutes in at least 50% of patients, Gregg C. Fonarow, MD, and his associates reported at the International Stroke Conference, sponsored by the American Heart Association.

Patient outcomes improved

The analyses they reported also documented how these most recent gains

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DBS provides long-term benefits for patients with Parkinson's disease

LAS VEGAS—Deep brain stimulation (DBS) provides motor and nonmotor benefits at 6 months, 1 year, and 2 years after implantation in patients with Parkinson's disease, according to a large-scale collection of outcome data. The treatment improves motor function and quality of life and has an acceptable safety profile. The analysis was presented at the annual meeting of the North American Neuromodulation Society.

Research by Okun et al. in 2012 and Schuepbach et al. in 2013 demonstrated that DBS effectively reduces the motor complications of Parkinson's disease. To monitor the treatment's efficacy and safety on a large scale, investigators established a prospective registry of patients with levodopa-responsive Parkinson's disease who underwent DBS implantation. An aim of the registry is to improve understanding of the clinical use and outcomes of DBS in this population. As many as 1,000 patients have been implanted with

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Routine clinical data may predict psychiatric adverse effects from levetiracetam

Among patients with epilepsy, a simple model may help guide prescription in clinical practice.

Among patients with epilepsy, a simple model that incorporates factors such as a patient's sex and history of depression, anxiety, and recreational drug use may help predict the risk of a psychiatric adverse effect from levetiracetam, according to a study published in *JAMA Neurology*.

"This study derived 2 simple models that predict the risk of a psychiatric adverse effect from levetiracetam" and can "guide prescription in clinical practice," said Colin B. Josephson, MD, of the department of clinical neurosciences at the University of Calgary (Canada) and his research colleagues.

Levetiracetam is a commonly used first-line treatment for epilepsy because of its ease of use, broad spectrum of action, and safety profile, the researchers said. Still, psychiatric adverse reactions occur in as many as 16% of patients and frequently require treatment discontinuation.

To evaluate whether routine clinical data can predict which patients with epilepsy will experience a psychiatric adverse event from levetiracetam, the investigators analyzed data from The Health Improvement Network (THIN) database, which includes anonymized patient records from general practices in the United Kingdom. They assessed 21 variables for possible inclusion in prediction models. They identified these variables by searching the literature and weighing input from a panel of experts.

Their analysis included data from Jan. 1, 2000–May 31, 2012. Among the more than 11 million patients in THIN, the researchers identified 7,300 incident cases of epilepsy. The researchers examined when patients received a first prescription for levetiracetam and whether patients experienced a psychiatric symptom or disorder within 2 years of the prescription.

Among 1,173 patients with epilepsy receiving levetiracetam, the median age was 39 years; about half were women. In all, 14.1% experienced a psychiatric symptom or disorder within 2 years of prescription. Women were more likely to report a psychiatric symptom (odds ratio, 1.41), as were patients with a history of social deprivation (OR, 1.15), anxiety (OR, 1.74), recreational drug use (OR, 2.02), or depression (OR, 2.20).

> A patient's sex and history of depression are among the factors that predict the likelihood of adverse effects.

The final model included female sex, history of depression, history of anxiety, and history of recreational drug use. Low socioeconomic status was not included because "it would be challenging to assign this score in clinic," the authors said.

"There was a gradient in risk probabilities increasing from 8% for 0 risk factors to 11%–17% for 1, 17% to 31% for 2, 30%–42% for 3, and 49% when all risk factors were present," Dr. Josephson and his colleagues indicated. "The discovered incremental probability of reporting a psychiatric sign can help generate an index of suspicion to counsel patients."

Using the example of a woman patient with depression, the model "suggests she would be at risk," with a 22% chance of a psychiatric adverse event in the 2 years after receiving a levetiracetam prescription.

The researchers created a second prediction algorithm based on data from patients without documentation of a mental health sign, symptom, or disorder prior to their levetiracetam prescription. This model incorporated age, sex, recreational drug use, and levetiracetam daily dose; it performed comparably well and might be used to determine safety of prescription, according to Dr. Josephson and his colleagues.

The authors noted that the study was limited by an inability to evaluate medication adherence and seizure type and frequency. One advantage of the study's design is that it may have circumvented expectation bias because general practitioners were not prone to anticipating psychiatric adverse events or to have a lower threshold for diagnosing them.

The authors disclosed research fellowships and support from foundations and federal agencies. **NR**

—Jake Remaly

Suggested Reading

Josephson CB, Engbers JDT, Jette N, et al. Prediction tools for psychiatric adverse effects after levetiracetam prescription. *JAMA Neurol.* 2019 Jan 28 [Epub ahead of print].

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Bioequivalent generic formulations of lamotrigine and levetiracetam control new-onset focal seizures equally well

Reproductive and mental health histories can help decide which antiepileptic drug is the better choice for an individual patient.

NEW ORLEANS—Bioequivalent generic formulations of levetiracetam and lamotrigine reduced seizures by a similar extent over 2 years in a retrospective study of patients with newly diagnosed focal epilepsy.

Each drug had a specific adverse event profile, with lamotrigine associated with rash and levetiracetam with mood disorders, Sirichai Chayasirisobhon, MD, said at the annual meeting of the American Epilepsy Society. This finding can influence the initial therapeutic decision, said Dr. Chayasirisobhon, who is affiliated with Kaiser Permanente Southern California. "If someone comes in with depression or mood disorder, I will start on lamotrigine, not levetiracetam. And we can decrease the chance of rash with a very slow titration, starting with just 5 mg/kg and working up over 6 months."

Although the drugs have a somewhat similar teratogenic profile, Dr. Chayasirisobhon added that he favors lamotrigine for women of childbearing years. "It's a little bit better choice for them, I think."

His retrospective analysis followed 442 patients from first seizure and medical therapy for 2 years. The generic medications were dispensed from Kaiser Permanente's central pharmacy. They were single-source, with a proven 95% bioequivalence. The main outcome was the percentage of patients who became seizure free and remained so. Any seizure, whether febrile, breakthrough, or from titration, was considered a failure. These patients were dropped from the study. Any patient who developed a drug-related rash was dropped from the study and started on another medication.

More women than men took lamotrigine (113 vs. 75), whereas more men took levetiracetam (148 vs. 106). Those taking lamotrigine were younger than were those taking levetiracetam (30 vs. 40 years).

> At the end of 2 years, there was no statistically significant difference in the primary outcome of seizure freedom (66.5% with lamotrigine vs. 72.4% with levetiracetam).

At the end of 2 years, there was no statistically significant difference in the primary outcome of seizure freedom (66.5% with lamotrigine vs. 72.4% with levetiracetam). In the lamotrigine group, 33.5% were eliminated from the study, 24% because they had a seizure, and the rest due to an adverse event. In the levetiracetam group, 27.6% were eliminated, 13% because they had a seizure, and the rest because of an adverse event.

Adverse events in the lamotrigine group included rash (12), dizziness (3), lethargy (1), and mood changes (2). Among the levetiracetam group, adverse events included dizziness (3), lethargy (7), mood changes (20), slowed thinking (4), depression (2) and headache (1).

"Rash was the main adverse event we saw in this group, and this was even when we did a very slow titration of 5 mg/kg per week," Dr. Chayasirisobhon said. Patients were instructed to stop the medication immediately and contact the prescribing physician at any sign of rash or itching. "Fortunately, we had no cases of Stevens-Johnson syndrome, and all our cases of rash were transient." In the levetiracetam group, however, mood changes were a major issue. "Some of the patients became very agitated and aggressive. Whenever we see a patient for the first time, we always ask about mood changes, and we instruct the family to call and report any changes in mood immediately."

For new patients of reproductive age, Dr. Chayasirisobhon generally prefers to start levetiracetam. Its safety profile is remarkable, he said, recounting a case report he published in 2010. The paper described a male patient who decided to commit suicide after an argument with his wife. He took his levetiracetam and walked to his father's grave, swallowing pills the entire time. When he arrived at the grave, he had taken around 65 g of the medication. "The amazing thing was, he's still walking, just a little unsteady. Then he decided he's not ready to die," Dr. Chayasirisobhon said. "He was able to call 911, so he's still talking fine. When they checked his level it was so high, but he remained unimpaired except for the unsteady gait and some nystagmus."

The study did not receive outside funding. Dr. Chayasirisobhon had no financial disclosures. **NR**

— Michele G. Sullivan

Suggested Reading

Chayasirisobhon S, Chayasirisobhon WV, Tsay CC. Acute levetiracetam overdose presented with mild adverse events. *Acta Neurol Taiwan.* 2010;19(4):292-295.

No evidence for disease-modifying effect of levodopa in Parkinson's disease

In the delayed-start LEAP study, researchers evaluated patients with early Parkinson's disease over the course of 80 weeks.

Levodopa did not significantly alter the course of Parkinson's disease in a randomized, 80-week, delayed-start clinical trial, investigators reported. The disease course was not significantly different for patients who had a full 80 weeks of levodopa/carbidopa therapy, compared with that seen in those who started treatment after a 40-week delay, according to the investigators.

"These findings imply that levodopa had no disease-modifying effect on Parkinson's disease over the period of the trial," wrote investigator Rob M. A. de Bie, MD, PhD, professor of movement disorders at the University of Amsterdam, and his colleagues in the *New England Journal of Medicine*.

By contrast, results of an earlier randomized, placebo-controlled trial suggested that levodopa had disease-modifying effects, though the findings of that study were inconclusive, according to authors of an editorial.

The LEAP trial

In the current multicenter trial, known as LEAP (Levodopa in Early Parkinson's Disease) a total of 445 patients with early Parkinson's disease were randomized to either 80 weeks of levodopa and carbidopa or to 40 weeks of placebo, followed by 40 weeks of levodopa/carbidopa.

Levodopa was dosed at 100 mg three times per day, and carbodopa at 25 mg three times per day, according to the report.

There was no significant difference between the early and delayed treatment groups for the primary outcome, which was change in the Unified Parkinson's Disease Rating Scale (UPDRS) from baseline to week 80.

The mean change in UPDRS was –1.0 in the group of patients who had the full 80 weeks of levodopa/carbidopa and –2.0 for those who had delayed therapy, for a difference of 1 point (P = .44). Higher scores on the UPDRS signify worse disease.

At week 40, there was a change in UPDRS favoring the early-initiation strategy, which reflected the effects of levodopa on disease symptoms, investigators added.

> **The study provides no evidence to suggest that levodopa slows Parkinson's disease progression. Nor does it provide evidence that clinicians should delay therapy when it is clinically indicated.**

Nausea was more common in the early-start group during the first 40 weeks of the trial. However, there were no differences between groups in other adverse events of particular interest, including dyskinesias and motor fluctuations related to levodopa, Dr. de Bie and his colleagues reported.

Taken together, these results suggest no beneficial or detrimental disease-modifying effect for an early treatment strategy, although further trials are warranted to evaluate other strategies, such as higher levodopa doses, longer administration, or starting the drug at later stages of disease, they wrote.

LEAP supports today's practice standards

This trial supports current clinical practice in two ways, according to Susan Bressman, MD, and Rachel Saunders-Pullman, MD, MPH. On one hand, the study provides no evidence to suggest that levodopa slows Parkinson's disease progression, Drs. Bressman and Saunders-Pullman wrote in an accompanying editorial. On the other hand, they added, it provides no evidence that clinicians should delay therapy when it is clinically indicated.

Rob M. A. de Bie, MD, PhD

The LEAP trial was designed to resolve uncertainty over the potential effects of levodopa on disease progression, they noted. This was necessary because of the results of the placebo-controlled ELLDOPA trial, which was published about 14 years ago and suggested that patients randomized to 40 weeks of levodopa did not deteriorate clinically to the degree that was observed in patients randomized to placebo.

The primary end point of that trial was UPDRS scores after a 2-week washout period.

While one interpretation of the UPDRS results from ELLDOPA was that levodopa slowed disease progression, another was that the 2-week washout period was too short, allowing for residual effects of levodopa on symptoms, suggested Dr. Bressman and Dr. Saunders-Pullman, both of the Icahn School of Medicine at Mt. Sinai, New York.

The randomized LEAP study now shows not only that there were no differences in UPDRS scores when using a delayed start trial design—which implies that there was no disease-modifying effect—but also that starting levodopa early did not have negative effects, the editorial authors wrote.

In particular, the researchers showed no differences in rates of dyskinesia or levodopa-related fluctuations in those started early versus those started later.

"The results of the current trial, taken together with those of other trials, support treatment that is guided by clinical need and that uses the lowest dose that provides a satisfactory clinical effect," the editorialists wrote.

Dr. de Bie reported grants from ZonMw, Parkinson Vereniging, and Stichting Parkinsonfonds during the conduct of the study, as well as grants from GE Health and Medtronic outside the submitted work. Study authors provided disclosures related to Netherlands Organization for Scientific Research, Michael J. Fox Foundation, UCB, AbbVie, Boston Scientific, Biogen, Merck, and others.

Dr. Bressman reported disclosures related to Denali Therapeutics, the Michael J. Fox Foundation, and Prevail Therapeutics, while Dr. Saunders-Pullman reported disclosures with Denali Therapeutics, the National Institutes of Health, Genzyme Sanofi, and the Bigglesworth Family Foundation. **NR**

—Andrew D. Bowser

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Bressman S, Saunders-Pullman R. When to start levodopa therapy for Parkinson's disease. *N Engl J Med.* 2019;380(4):389-390.

Verschuur CVM, Suwijn SR, Boel JA, et al. Randomized delayed-start trial of levodopa in Parkinson's disease. *N Engl J Med.* 2019;380(4):315-324.

Benefit of thrombectomy may be universal

The proportional benefit of thrombectomy is uniform among various subgroups of patients with acute ischemic stroke.

Age, symptom severity, and serum glucose do not influence the benefit of endovascular thrombectomy for patients with stroke, according to research published online ahead of print Jan. 28 in *JAMA Neurology*. The location of the arterial occlusive lesion and the imaging technique used to select patients for the procedure also do not influence the therapy's benefits, the researchers said. Although the proportional benefit of thrombectomy plus medical management is uniform across subgroups, compared with medical management alone, patients may have different amounts of absolute benefit.

The results of the DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) trial, which were published in 2018, indicated that endovascular thrombectomy provided clinical benefits for patients with acute ischemic stroke if administered at 6-16 hours after stroke onset. As part of the trial's prespecified analyses, Maarten G. Lansberg, MD, PhD, associate professor of neurology and neurological sciences at Stanford University Medical Center in California, and his colleagues sought to determine whether thrombectomy had uniform benefit among various patient subgroups (e.g., elderly people, patients with mild symptoms, and those who present late after onset).

A total of 296 patients were enrolled in the randomized, open-label, blinded-endpoint DEFUSE 3 trial at 38 sites in the United States. Eligible participants had acute ischemic stroke resulting from an occlusion of the internal carotid artery or middle cerebral artery and evidence of salvageable tissue on perfusion CT or MRI. In all, 182 patients met these criteria and were randomized and included in the intention-to-treat analysis. The researchers stopped DEFUSE 3 early because of efficacy.

The study's primary endpoint was functional outcome at day 90, as measured with the modified Rankin Scale. Dr. Lansberg and his colleagues performed multivariate ordinal logistic regression to calculate the adjusted proportional association between endovascular treatment and clinical outcome among participants of various ages, baseline stroke severities, periods between onset and treatment, locations of the arterial occlusion, and imaging modalities, such as CT or MRI, used to identify salvageable tissue.

The population's median age was 70 years, and 51% of participants were women. The median National Institutes of Health Stroke Scale (NIHSS) score was 16. When the researchers considered the whole sample, they found that younger age, lower baseline NIHSS score, and lower serum glucose level independently predicted better functional outcome. The common odds ratio for improved functional outcome with endovascular therapy, adjusted for these variables, was 3.1. Age, NIHSS score, time to randomization, imaging modality, and location of the arterial occlusion did not interact significantly with treatment effect.

> **Younger age, lower baseline NIHSS score, and lower serum glucose level independently predicted better functional outcome. The adjusted common odds ratio for improved functional outcome with endovascular therapy was 3.1.**

"Our results indicate that advanced age, up to 90 years, should not be considered a contraindication to thrombectomy, provided that the patient is fully independent prior to stroke onset," said the researchers. "Although age did not modify the treatment effect, it was a strong independent predictor of 90-day disability, which is consistent with prior studies of both tissue plasminogen activator and endovascular therapy."

The trial's small sample size may have allowed small differences between groups to pass unnoticed, said the reseachers. Other trials of late-window thrombectomy will be required to validate these results, they concluded.

The National Institute for Neurological Disorders and Stroke supported the study through grants. Several investigators received consulting fees from and hold shares in iSchemaView, which manufactures the software that the investigators used for postprocessing of CT and MRI perfusion studies. Other authors received consulting fees from various pharmaceutical and medical device companies, including Genentech, Medtronic, Pfizer, and Stryker Neurovascular.

NR

—Erik Greb

Suggested Reading

Lansberg MG, Mlynash M, Hamilton S, et al. Association of thrombectomy with stroke outcomes among patient subgroups: secondary analyses of the DEFUSE 3 randomized clinical trial. *JAMA Neurol.* 2019 Jan 28 [Epub ahead of print].

NEWSROUNDUP

A high risk of life-threatening injury among patients with epilepsy

Patients with epilepsy have a high risk of life-threatening injury, according to a study published online ahead of print Feb. 5 in *Epilepsia*. Investigators performed a retrospective nested case–control study on patients enrolled in the Tasmanian Epilepsy Register from July 1, 2001, to June 30, 2002. The primary outcome measures were lifetime and recent 12-month injury. In all, 819 patients with epilepsy were included in the study. Ten percent of patients had an injury in the preceding year. Before adjusting for seizure frequency, any seizure over the past 12 months was associated with recent injury (adjusted odds ratio, 7.90). Impaired awareness, cluster seizures, sleep-only seizures, and convulsive seizure significantly influenced injuries, irrespective of seizure frequency.

Tan M, Boston R, Cook MJ, D'Souza WJ. Risk factors for injury in a community-treated cohort of patients with epilepsy in Australia. *Epilepsia*. 2019 Feb 5 [Epub ahead of print].

Race and ethnicity affect survival in Alzheimer's disease

Hispanic-American patients with Alzheimer's disease tend to survive significantly longer than patients of other ethnic or racial groups with the disease, according to a study published in the February issue of *Alzheimer's & Dementia*. Researchers examined 1,625 brain tissue samples and compared the disease progression and duration in individuals who had identified themselves as Hispanic, non-Hispanic white, or African-American. Hispanic-American patients had symptoms characteristic of Alzheimer's disease at an average age of 70: a year or more earlier than the other groups. They were more likely to have family history of dementia and they had lower cognitive scores at the end of life. The average duration of Alzheimer's disease was 12 years for Hispanic-Americans, compared with nine years for non-Hispanic whites and eight years for African-Americans.

Babulal GM, Quiroz YT, Albensi BC, et al. Perspectives on ethnic and racial disparities in Alzheimer's disease and related dementias: Update and areas of immediate need. *Alzheimers Dement*. 2019;15(2):292-312.

Peripheral nerve stimulation reduces hand tremor

Noninvasive neuromodulation may improve activities of daily living in patients with essential tremor.

LAS VEGAS—In patients with essential tremor, peripheral nerve stimulation significantly improves hand tremor and activities of daily living, compared with sham treatment. In addition, sensors worn on the wrist can provide objective measures of tremor in the home environment, said the investigators, who presented their research at the annual meeting of the North American Neuromodulation Society.

The current hypothesis is that tremulous activity within a central tremor network causes essential tremor, but the specific mechanisms are unknown. Research suggests that invasive neuromodulation of deep brain structures within this tremor network provides clinical benefit. The question of whether noninvasive neuromodulation of the peripheral nerve inputs connected to this network is beneficial has received comparatively little attention, however.

Rajesh Pahwa, MD, movement disorders division chief at the University of Kansas Medical Center in Kansas City, and his colleagues examined the safety and efficacy of noninvasive neuromodulation for hand tremor in patients with essential tremor. To provide treatment, they used a wristband with three electrodes that targeted the median and radial nerves. The stimulation pattern was adjusted to interrupt each patient's tremulous signal in the clinical setting and at home. Participants were asked to hold a certain posture for 20 seconds while the device recorded tremor frequency. After determining the peak tremor frequency, the device was able to adapt stimulation parameters to each patient.

Dr. Pahwa and his colleagues conducted an acute in-office study and an at-home study. In the in-office study, 77 participants were randomized to peripheral nerve treatment or sham stimulation of the tremor-dominant hand. The researchers evaluated tremor before and after one stimulation session using the Essential Tremor Rating Assessment Scale (TETRAS) Upper Limb Tremor Scale and the TETRAS Archimedes Spiral Rating Scale. In the at-home study, 61 participants were randomized to stimulation, sham, or standard of care for 2 weeks. After that point, all participants underwent two to five 40-minute stimulation sessions daily for 2 weeks. Patients in the treatment and sham groups had at least two sessions per day.

In the in-office study, the researchers randomized 40 patients to stimulation and 37 patients to sham. Dr. Pahwa and his colleagues determined that participants had been blinded successfully. The investigators observed a mean improvement in forward posture of approximately 0.75 points among treated patients, compared with a mean improvement of 0.3 points in the sham group. The difference between groups was statistically significant. Treated patients had significant improvements in upper limb tremor score and total performance score, compared with the sham group. The investigators also observed greater mean improvements in spiral drawing, lateral posture, and movement among treated patients, compared with the sham group, but the differences were not statistically significant.

> **Patients treated with peripheral nerve stimulation had significant improvements in upper limb tremor score and total performance score, compared with the sham participants.**

Participants in the in-office study rated their improvement on activities of daily living. Average improvement across tasks was significantly greater for the treated group, compared to the sham group. Improvement on each individual task also was greater for the treated group than the sham group. The differences in improvement were significant for holding a cup of tea, dialing a telephone, picking up change, and unlocking a door with a key.

Rajesh Pahwa, MD

In the at-home study, the decrease in tremor amplitude, as measured by the wrist-worn device, was significantly greater among participants who received stimulation than in the sham group. "These randomized, controlled studies suggest that noninvasive peripheral neuromodulation may offer meaningful symptomatic relief from hand tremor in essential tremor with a favorable safety profile, compared to other available therapies," noted Dr. Pahwa and his colleagues. "At-home monitoring may provide key insights into evaluating and treating tremor," they added.

The studies were supported by Cala Health.

NR

—Erik Greb

NEWSROUNDUP

Midlife activity may reduce risk of later dementia

Physical and mental activity in middle age may be associated with a lower risk of dementia in later life, according to a study published online ahead of print February 20 in *Neurology*. Researchers examined 800 Swedish women with an average age of 47 years and followed them for 44 years. Participants were asked at baseline about their mental and physical activities. Mental activities included reading and writing, singing in a choir, gardening, and club activities. Physical activity ranged from walking or biking to engaging in competitive sports. During the study, 194 women developed dementia. Women with a high level of mental activities were 46% less likely to develop Alzheimer's disease and 34% less likely to develop dementia overall than the women with a low level of mental activities. Physically active women were 52% less likely to develop dementia with cerebrovascular disease and 56% less likely to develop mixed dementia than the inactive women.

Najar J, Östling S, Gudmundsson P, et al. Cognitive and physical activity and dementia: a 44-year longitudinal population study of women. *Neurology*. 2019 Feb 20 [Epub ahead of print].

Evidence suggests a Parkinson's disease pandemic

By 2040, the number of people with Parkinson's disease may increase to more than 12 million, according to research published December 18, 2018, in a supplement to the *Journal of Parkinson's Disease*. The increase will result principally from aging, said the investigators, but additional factors, including increasing longevity, declining smoking rates, and increasing industrialization, could increase the affected population to more than 17 million. The recent Global Burden of Disease study indicated that age-standardized rates of Parkinson's disease increased for every region of the world between 1990 and 2016. Overall, age-standardized prevalence rates increased worldwide by nearly 22%. Evidence from analyses of global surveys, medical records of large institutions, national census bureaus, and death certificates suggests that the incidence of Parkinson disease may be rising.

Dorsey ER, Sherer T, Okun MS, Bloem BR. The emerging evidence of the Parkinson pandemic. *J Parkinsons Dis*. 2018;8(s1):S3-S8.

Intensive insulin added no benefit for hyperglycemia after ischemic stroke

Intensive and standard insulin regimens produced similar clinical outcomes after an acute ischemic stroke.

HONOLULU—In patients who were hyperglycemic following an acute ischemic stroke, intensive insulin control using a continuous insulin drip and an aggressive blood glucose target of 80-130 mg/dL provided no incremental benefit in clinical outcome, compared with a standard approach of serial, subcutaneous insulin injections and a moderate blood glucose target, in a multicenter U.S. trial with more than 1,100 patients.

The results highlighted the potential downside to aggressive insulin treatment: with an associated 2.6% incidence of severe hypoglycemia, defined as blood glucose falling below 40 mg/dL, said Karen C. Johnston, MD, at the International Stroke Conference sponsored by the American Heart Association."Our data suggest that subcutaneously administered insulin with a target blood glucose level of less than 180 mg/dL is the preferred treatment" because it produces similar efficacy without causing severe hypoglycemia, concluded Dr. Johnston, professor and chair of neurology at the University of Virginia in Charlottesville. "There should be no further debate" over the potential superiority of a glucose target substantially below 180 mg/dL, she added in an interview.

Continuing to use a glucose target of less than 180 mg/dL and treating patients with subcutaneous insulin injections every 6 hours to achieve it will mean substantially less resource use and preclude the need for keeping patients in intensive care beds, as is needed with an insulin drip, Dr. Johnston noted. A treatment target of less than 180 mg/dL is also consistent with the most recent American Heart Association stroke treatment guidelines, which listed a blood glucose target of 140-180 mg/dL as a class IIa recommendation.

The Stroke Hyperglycemia Insulin Network Effort (SHINE) trial enrolled 1,151 adults diagnosed with an acute ischemic stroke at 63 U.S. centers during 2012-2018, excluding patients with type 1 diabetes. Patients had to enter the study within 12 hours of their last known well time, and with an elevated blood glucose level (i.e., above 110 mg/dL in patients with type 2 diabetes or 150 mg/dL or higher in other patients). The median glucose level of enrolled patients was about 188 mg/dL. Enrolled patients averaged 66 years old, and about 80% had type 2 diabetes. The median time from last known well to randomization was just over 7 hours. Almost two-thirds of the patients received thrombolytic treatment, and about 13% underwent thrombectomy.

During as many as 72 hours of treatment following enrollment, the patients in the standard-treatment arm showed a fairly steady average blood glucose level of 179 mg/dL; patients in the intensive arm showed a steady average of 118 mg/dL.

The study's primary end point was the percentage of patients with a favorable outcome 90 days after enrollment, based on their modified Rankin scale score at that time. The scores that qualified for this end point varied depending on stroke severity at baseline. The percentage of patients achieving a favorable outcome was 20.5% among the intensive patients and 21.6% among those who received standard insulin treatment, a difference that was not statistically significant.

The findings left open the question of how best to manage acute ischemic stroke patients who present with hyperglycemia. "Hyperglycemic stroke patients have worse outcomes than stroke patients without hyperglycemia. More aggressively treating the hyperglycemia did not help these patients, We need to figure out what will help them," Dr. Johnson said. **NR**

—Mitchel L. Zoler

Risk factors for PTSD and depression after mild TBI

A history of mental illness increases the likelihood of these outcomes.

Civilian patients with mild traumatic brain injury (TBI) who are black, have psychiatric history or lower education, or whose injury was caused by assault might be at greater risk of developing posttraumatic stress disorder (PTSD) or major depression, a longitudinal study suggests.

"Our findings may have implications for surveillance and treatment of mental disorders after TBI," wrote Murray B. Stein, MD, MPH, distinguished professor of psychiatry and family medicine and public health at the University of California, San Diego, and his associates. The study was published Jan. 30 in *JAMA Psychiatry*.

The researchers looked at the risk factors for and prevalence of PTSD and major depressive disorder (MDD) among 1,155 patients who were evaluated for mild TBI in emergency departments at 11 level 1 trauma centers across the United States. The patients were enrolled in the prospective Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study.

Each additional year of education was associated with a significant 11% reduction in the risk of developing PTSD after mild TBI. Also, black patients had a greater than fivefold higher risk of PTSD, compared with individuals who were not black.

Patients with a history of mental illness and those who had experienced their injury as a result of assault or violence—as opposed to a motor vehicle accident or fall, for example—had a greater than threefold higher risk of developing PTSD (odds ratios, 3.57 and 3.43, respectively).

Having less education, being black, and history of mental illness were associated with an increased risk of MDD after mild TBI. Duration of lost consciousness or posttraumatic amnesia, evidence of brain injury on CT, or hospitalization did not predict PTSD or MDD.

"Although MDD and PTSD are prevalent after TBI, little is known about which patients are at risk for developing them," Dr. Stein and his associates wrote. A prior mental health problem was an "exceptionally strong" risk factor, which "underscores the importance of clinicians being aware of the mental health history of their patients with [mild TBI], as this information is central to expectations regarding both short-term and long-term outcome," they said.

Dr. Stein and his associates cited as a limitation their reliance on patient or family report. In addition, the elevated risk among black individuals, which was independent of socioeconomic status or cause of injury, is not understood. "Unmeasured covariates may be part of the explanation; this is a topic needing further study," they wrote.

The study was supported by the National Institutes of Health, the U.S. Department of Defense, Abbott Laboratories, and One Mind. Four authors declared consultancies, advisory board positions, speaking fees, and shares or stock options with the pharmaceutical and private industry. Two authors declared grants from the study sponsors. **NR**

—Bianca Nogrady

Suggested Reading

Stein MB, Jain S, Giacino JT, et al. Risk of posttraumatic stress disorder and major depression in civilian patients after mild traumatic brain injury: a TRACK-TBI study. *JAMA Psychiatry.* 2019 Jan 30 [Epub ahead of print].

Cilostazol plus aspirin or clopidogrel reduces the risk of recurrent stroke

Dual therapy with cilostazol and aspirin or clopidogrel did not increase the risk of serious bleeding.

HONOLULU—A combination of cilostazol and aspirin or clopidogrel reduces the risk of recurrent ischemic stroke, compared with aspirin or clopidogrel alone, among patients at high risk for recurrent stroke. The combination also entails a similar risk of major bleeding, compared with aspirin and clopidogrel alone, according to results from the Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS.com).

Dual-antiplatelet therapy with aspirin and clopidogrel reduced the rate of recurrent stroke in previous studies. The benefit of this drug combination is relatively short-lived, however, and long-term concomitant use of aspirin and clopidogrel entails a risk of major bleeding. Other data have indicated

The benefit of dual therapy with aspirin and clopidogrel is relatively short-lived

that cilostazol, which is approved by the Food and Drug Administration to alleviate intermittent claudication in patients with peripheral vascular disease, prevents stroke recurrence without increasing the incidence of serious bleeding, compared with aspirin, said Kazunori Toyoda, MD, PhD, who presented the results of the CSPS.com trial at the International Stroke Conference sponsored by the American Heart Association.

Dr. Toyoda of the National Cerebral and Cardiovascular Center in Osaka, Japan, and his colleagues randomized 1,879 high-risk patients at 8-180 days after the onset of noncardioembolic ischemic stroke identified on MRI to receive 81 or 100 mg aspirin or 50 or 75 mg clopidogrel alone, or a combination of cilostazol 100 mg twice daily with aspirin or clopidogrel. They conducted their open-label, parallel-group trial at 292 sites in Japan from December 2013 through March 2017.

To be considered at high risk, participants had to meet one or more of the following criteria: 50% or greater stenosis of a major intracranial artery, 50% or greater stenosis of an extracranial artery, and two or more vascular risk factors. The trial's primary efficacy outcome was the first recurrence of ischemic stroke. Safety outcomes included severe or life-threatening bleeding.

The investigators ended the trial early because of a delay in recruiting patients. They enrolled 1,884 and randomized 1,879 of an anticipated 4,000 patients. At randomization, 41% in the dual-therapy group received aspirin and 59% clopidogrel, and in the monotherapy group, 40% received aspirin and 60% clopidogrel. Baseline characteristics were similar between the treatment groups. The population's mean age was 70. Approximately 30% of patients were women.

> **The annual rate of recurrent ischemic stroke was 2.2% in patients receiving dual therapy and 4.5% in patients who received monotherapy.**

During a median follow-up period of 17 months, ischemic stroke recurred in 29 of 932 patients receiving dual therapy including cilostazol, for an annual rate of 2.2%, and in 64 of 947 patients receiving monotherapy, for an annual rate of 4.5% (hazard ratio, 0.49; 95% confidence interval, 0.31-0.76; P = .001). Severe or life-threatening bleeding occurred in 8 patients (0.6% per year) receiving dual therapy and 13 patients (0.9% per year) receiving monotherapy (HR, 0.66; 95% CI, 0.27-1.60; P = .354).

The study was funded by Otsuka Pharmaceutical, which manufactures cilostazol. Dr. Toyoda reported receiving support from Bayer Yakuhin, Daiichi Sankyo, Bristol-Myers Squibb, and Nippon Boehringer Ingelheim. **NR**

—Erik Greb

Deferoxamine does not improve 90-day outcomes after ICH

The drug is safe, and data suggest that it could improve 180-day outcomes.

HONOLULU—Deferoxamine mesylate does not significantly improve 90-day outcomes after intracranial hemorrhage (ICH), according to trial results described at the International Stroke Conference sponsored by the American Heart Association. However, the drug is safe and well tolerated, and data suggest that it may improve outcomes at 180 days.

Animal studies indicate that iron, which is released from hemolyzed red blood cells, accumulates in the brain after ICH and is associated with secondary neuronal injury and death. Researchers have found that deferoxamine, an iron chelator, provides neuroprotection and improves recovery after experimental ICH. The drug also has anti-inflammatory, antiapoptotic, and BP-lowering effects. Deferoxamine has been approved since the 1960s.

Researchers conducted a futility analysis

Magdy H. Selim, MD, PhD, a neurologist at Beth Israel Deaconess Medical Center in Boston, and colleagues hypothesized that treatment with deferoxamine could improve outcomes in patients with ICH. The researchers conducted a phase 2 clinical trial to evaluate whether deferoxamine should be studied in a phase 3 efficacy trial. In their multicenter, double-blind study, Dr. Selim and his colleagues randomized patients with spontaneous supratentorial ICH in equal groups to 32 mg/kg per day of deferoxamine or saline placebo. Treatments were administered as intravenous infusions for 3 consecutive days, and therapy was initiated within 24 hours after ICH onset. The follow-up period was 6 months.

Eligible participants had an National Institutes of Health Stroke Scale score of 6 or higher, a Glasgow Coma Scale score greater than 6, and had been functionally independent before the hemorrhage. The researchers excluded patients with a secondary cause for ICH or coagulopathy.

The primary endpoint in the futility analysis was the proportion of participants with a good clinical outcome—defined as a modified Rankin Scale (mRS) score of 0-2—at 90 days and 180 days. The secondary endpoint was good outcome, defined as an mRS score of 0-3, at 90 days. Safety endpoints included all deferoxamine-related adverse events until day 7 or discharge (whichever was earlier) and serious adverse events through day 90.

Data do not support a phase III study

Dr. Selim and his colleagues enrolled 294 participants in their trial, 3 of whom did not receive treatment. Of these included participants, 147 (50.5%) were randomized to placebo and 144 (49.5%) were randomized to deferoxamine. Participants' mean age was 60.3 years, and 38.5% of the population was female.

Overall, the two study arms did not differ significantly according to demographic and clinical characteristics, however, there were more nonwhite patients in the deferoxamine arm than in the placebo arm. In addition, thalamic hemorrhage and intraventricular hemorrhage were more common in the placebo-treated group and hemorrhages in the putamen and basal ganglia were more common in the deferoxamine-treated group.

Magdy H. Selim, MD, PhD

The rates of adverse events were comparable between the two study arms. Dr. Selim and his colleagues found no unexpected safety issues. Mortality was low, and the 90-day and 180-day mortality rates were comparable between the two treatment arms.

Approximately 34% of deferoxamine-treated patients and 33% of placebo-treated patients had an mRS score of 0-2 at 90 days. The adjusted absolute risk difference between arms was 0.6%; this result did not surpass the predefined futility threshold. The risk difference between groups for mRS score of 0-2 at 180 days was 8.6% in favor of deferoxamine, which did surpass the futility threshold.

The risk difference for meeting the secondary endpoint was 6.2% in favor of deferoxamine; this result did not surpass the futility threshold. Patients in both treatment groups improved between day 90 and day 180. The likelihood of good outcome was approximately 10% higher in the deferoxamine group at day 90 and 26% higher in the deferoxamine group at day 180.

"It is futile to conduct a phase 3 trial with the anticipation that treatment with deferoxamine would improve outcome, defined as mRS score of 0-2 at 90 days," said Dr. Selim. "These data, together with the data from MISTIE and CLEAR, suggest that ICH trials need to have a longer follow-up period to capture the full extent of recovery after ICH. Several of our secondary analyses tended to favor deferoxamine over the placebo arm and leave open the possibility that deferoxamine might lead to improved outcome at 180 days."

The researchers received support from the NIH and the National Institute of Neurological Disorders and Stroke.

NR

—Erik Greb

MENTALFLOSS

Nighttime rocking improves sleep and memory consolidation

A rocking motion not only leads to better sleep, but also improves memory consolidation during sleep, according to a study published Feb. 4 in *Current Biology*. "Having a good night's sleep means falling asleep rapidly and then staying asleep during the whole night," said Laurence Bayer, a biologist at the University of Geneva. "Our volunteers—even if they were all good sleepers—fell asleep more rapidly when rocked and had longer periods of deeper sleep associated with fewer arousals during the night. We thus show that rocking is good for sleep."

Eighteen healthy young adults underwent sleep monitoring in the researchers' laboratory. After a baseline night, the participants stayed two more nights: one sleeping on a gently rocking bed and the other sleeping on an identical bed that did not move. The data showed that participants fell asleep faster while they were rocking. Once asleep, they also spent more time in non-REM sleep, slept more deeply, and woke up less.

The researchers next sought to determine how improved sleep influences memory. To assess memory consolidation, the investigators asked participants to study word pairs. They measured participants' accuracy in recalling those paired words in an evening session, compared with during a session on the next morning when they woke up. They found that people performed better on the morning test when they had been rocked during sleep.

Perrault AA, Khani A, Quairiaux C, et al. Whole-night continuous rocking entrains spontaneous neural oscillations with benefits for sleep and memory. *Curr Biol*. 2019;29(3):402-411.

SPRINT MIND: Lowering blood pressure reduces the risk of cognitive impairment

A planned extension aims to add insights from 2 years of follow-up.

An extension of the SPRINT MIND hypertension trial will seek to prove the original study's tantalizing suggestion: that intensive blood pressure control decreases the risk of developing mild cognitive impairment (MCI) and dementia.

SPRINT MIND 2.0 will re-recruit SPRINT MIND subjects for follow-up cognitive and clinical tests. Participants will remain on their standard of care blood pressure regimens. An Alzheimer's Association announcement about the extension and the association's plan to fund the study with an $800,000 grant coincided with the publication of the SPRINT MIND results in *JAMA* on Jan. 28.

Investigators first presented SPRINT MIND results at the Alzheimer's Association International Conference in July, and the data sparked excitement in the dementia research community. Although the trial failed to meet its primary end point of reducing dementia incidence, two secondary end points provided evidence of efficacy. Patients who reduced their systolic blood pressure (SBP) to less than 120 mm Hg were 19% less likely to develop MCI and 17% less likely to develop all-cause dementia than were those who achieved a hypertension target of less than 140 mm Hg.

> Two secondary end points provide evidence of efficacy.

Researchers have suggested that the median 5-year follow-up was not long enough to show any significant effects on dementia, which can take years to fully manifest.

"SPRINT MIND 2.0 and the work leading up to it offers genuine, concrete hope," Maria C. Carrillo, PhD, chief science officer for the Alzheimer's Association, said in a press statement. "MCI is a known risk factor for dementia, and everyone who experiences dementia passes through MCI. When you prevent new cases of MCI, you are preventing new cases of dementia. The Alzheimer's Association finds these data to be compelling and is committed to getting clarity and certainty on the dementia outcome by following participants for a longer period of time."

The promise of prevention

The study strengthens a new and energetic push to find ways to prevent dementia, which has proven itself intractable in every drug study to date.

"This study is in line with where the field of dementia research is going: preventing memory loss earlier," said Laurie Ryan, PhD, chief of the dementias of aging branch in the National Institute on Aging (NIA). "Much like we have research-based interventions for heart health and cancer prevention, we hope to have guidance based on this and subsequent studies that will more definitively show how to slow or even stop dementia well before symptoms appear."

NIA director Richard J. Hodes, MD, agreed.

"Dementia continues to be a large public health challenge, and based on the primary results of this study, we still have yet to find an intervention strategy proven to reduce the risk of dementia," he said in a press statement. "Nevertheless, the secondary results showing that intensive lowering of blood pressure may reduce risk for MCI, a known risk factor for dementia, gives us additional avenues to explore on the path to prevention."

SPRINT MIND was a substudy of the Systolic Blood Pressure Intervention Trial (SPRINT). It compared two strategies for managing hypertension in older adults. The intensive strategy had a target of less than 120 mm Hg, while standard care had a target of less than 140 mm Hg. SPRINT showed that more intensive blood pressure control produced a 25% reduction in the composite primary composite end point of cardiovascular events, stroke, and cardiovascular death. SPRINT helped inform

Maria C. Carrillo, PhD

Jeff D. Williamson, MD

COMMENTARY
A 'major leap forward' in dementia prevention research

Kristine Yaffe, MD

SPRINT MIND offers hope that an achievable blood pressure goal can dramatically alter the trajectory from mild cognitive impairment to dementia, said Kristine Yaffe, MD, in an editorial accompanying the trial results in *JAMA*. But at this point, it's impossible to make specific clinical recommendations.

"There are some challenges regarding how to apply the SPRINT MIND results in clinical practice. The early termination of the trial and the extended follow-up as a cohort blurs what the effect size might have been if the intervention had continued as planned. The magnitude of the effect of intensive systolic blood pressure lowering might have been greater given that, during the cohort phase, which lasted about as long as the intervention phase, the systolic blood pressure differences between treatment groups declined."

In addition, it is not clear which hypertension treatment regimens were most effective in improving cognitive outcomes.

"Information necessary to compare the effects of classes of antihypertensive agents on cognitive outcomes is also not provided. SPRINT used a quasi-pragmatic approach with suggestions for treatment choice, but practitioners approached systolic blood pressure control individually, and most participants were taking multiple drugs."

Nevertheless, the positive secondary findings and the encouraging trajectory on dementia risk suggest that blood pressure management should be a cornerstone of dementia prevention algorithms.

"The SPRINT MIND study may not be the final approach for prevention of Alzheimer's disease or other cognitive impairment, but it represents a major leap forward in what has emerged as a marathon journey."

Dr. Yaffe is a professor of psychiatry, neurology, and epidemiology and the Roy and Marie Scola Endowed Chair in Psychiatry at the University of California, San Francisco.

Suggested Reading

Yaffe K. Prevention of cognitive impairment with intensive systolic blood pressure control. *JAMA.* 2019;321(6):548-549.

Trial compares two approaches to managing hypertension in older adults

the 2017 high blood pressure clinical guidelines from the American Heart Association and American College of Cardiology.

The SPRINT MIND substudy, headed by Jeff D. Williamson, MD, of Wake Forest University, Winston-Salem, NC, asked whether intensive management had any effect on probable all-cause dementia or MCI, as well as imaging evidence of changes in white matter lesions and brain volume. It followed patients for up to 7 years and comprised 9,361 SPRINT subjects at least 50 years old (mean, 68 years) with at least one cardiovascular risk factor. Nearly a third (30%) were black, and 10% Hispanic. The primary outcome was incident probable dementia. Secondary outcomes were MCI and a composite of MCI or probable dementia. About a third had a SBP of 132 mm Hg or less, another third had a systolic pressure of 132–145 mm Hg, and the remainder had a systolic pressure greater than 145 mm Hg.

Physicians could use their choice of antihypertensive treatments. The study protocol encouraged, but did not mandate, thiazide-type diuretics as a first-line agent, followed by loop diuretics and beta-adrenergic blockers. Chlorthalidone was encouraged as the primary thiazide-type diuretic, and amlodipine as the preferred calcium-channel blocker.

Effective control

The interventions successfully controlled blood pressure. The mean SBP was 121.6 mm Hg in the intensive therapy group and 134.8 mm Hg in the standard group. The difference between groups was statistically significant.

Dementia developed in 149 in the aggressive control group and 176 in the standard group—a nonsignificant difference of 17% (hazard ratio, 0.83). MCI developed in 287 in the intensive group and 353 in the standard treatment group, which was a statistically significant 19% reduction. There was also a significant 15% reduction in the composite outcome of MCI or probable dementia in favor of intensive treatment.

As evidenced by the Alzheimer's Association grant, dementia researchers have focused on SPRINT MIND's positive secondary endpoints. At the AAIC meeting, Dr. Williamson even suggested that antihypertensive medications could be seen as disease-modifying agents for cognitive decline.

"I think we can say this is the first disease-modifying strategy to reduce the risk of MCI," Dr. Williamson said during a press briefing. And although the primary end point—the 17% relative risk reduction for probable all-cause dementia—didn't meet statistical significance, "It's comforting to see that the benefit went in the same direction and was of the same magnitude." **NR**

—Michele G. Sullivan

Suggested Reading

Williamson JD, Pajewski NM, Auchus AP, et al. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA.* 2019; 321(6):553-561.

When to suspect a severe skin reaction to an AED

Although most eruptions are benign, certain symptoms raise concerns about rare and potentially fatal antiepileptic drug reactions.

NEW ORLEANS—Most skin eruptions in patients taking antiepileptic drugs (AEDs) are relatively benign. With close supervision, some patients with epilepsy may continue treatment despite having a benign drug rash, according to a lecture at the annual meeting of the American Epilepsy Society.

"When do you know that you're not dealing with that kind of eruption?" said Jeanne M. Young, MD, assistant professor of dermatology at the University of Virginia in Charlottesville. Dr. Young discussed when health care professionals should suspect rare, serious, and potentially fatal drug reactions that require patients to stop an AED immediately, such as drug rash with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN).

Signs and symptoms that raise concerns about severe cutaneous reactions include swelling of the face; lesions that are fluid-filled, dusky, or painful; mucus membrane involvement; and signs of systemic involvement.

Associations with anticonvulsants

Diffuse swelling of the face is a hallmark symptom of DRESS. Fluid-filled lesions such as pustules, vesicles, and bullae indicate a condition other than a benign drug eruption. Signs of systemic involvement may include fever, marked eosinophilia, transaminitis, and evidence of lymphocyte activation. "In general, I want to see systemic involvement that can't be explained by the patient's other systemic diseases," Dr. Young said.

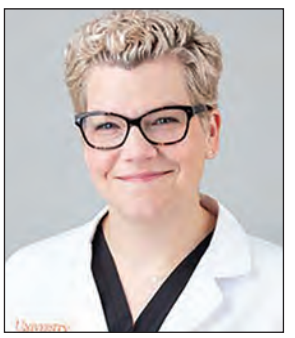
A 2018 study found that AEDs are associated with SJS and TEN, and the labels for lamotrigine and carbamazepine include black box warnings about the risk of severe cutaneous adverse events. Carbamazepine's warning, which was added in 2007, notes that SJS and TEN are significantly more common in patients of Asian ancestry with the human leukocyte antigen allele HLA-B*1502 and that physicians should screen at-risk patients before starting treatment.

Benign drug rashes

Morbilliform drug eruptions, sometimes called benign exanthems, are "by far the most common drug rash that we see" and typically are "the rashes that people refer to as drug rashes," Dr. Young said. The mechanisms appear to be primarily immune complex mediated and cell mediated. "When the drug is stopped, these rashes tend to go away quite predictably in 2–3 weeks."

> Morbilliform drug eruptions, sometimes called benign exanthems, are "by far the most common drug rash that we see" and typically are "the rashes that people refer to as drug rashes," said Jeanne M. Young, MD.

For any class of drug, about 1% of people taking that medication may have this type of reaction, Dr. Young said. "We expect to see erythematous papules and plaques that oftentimes become confluent on the skin." These reactions generally occur 7–10 days after the first exposure to the medication, and most patients do not have other symptoms, although the rash may itch. In addition, patients may have erythroderma with desquamation. "I think it's important to point out the difference between desquamation, which is loss of the stratum corneum, and epidermal sloughing, which is what you see in something like [SJS] or TEN, where you're actually losing the entire epidermis," Dr. Young said. Recovering from desquamation is "sort of like recovering from a sun burn, and it's not particularly dangerous." Management of morbilliform drug eruptions is largely symptomatic.



Jeanne M. Young, MD

Treat through, taper, or rechallenge

In the case a benign drug rash, "if you feel like you ... need to keep a patient on a drug, you do have that option with close supervision," Dr. Young said. "Communicate that with the dermatologist. Say, 'I have really struggled getting this patient stabilized. Can we keep them on this drug?' "

The dermatologist may not fully realize the implications of stopping an effective AED in a patient with seizures that have been difficult to control. If the drug rash is benign, treating through may be an option. Patients often resolve the rash while continuing the medication, which may be because of desensitization, Dr. Young said. If a patient's symptoms are too great to continue the drug, neurologists have the option of slowly tapering the drug and reinitiating with a new drug, Dr. Young said. Neurologists also may choose to rechallenge.

If a patient is on several medications, making it difficult to elucidate a causative agent, after stopping those drugs and allowing the rash to resolve, "there is little danger in restarting a medication," she said.

Benign rash or DRESS?

"When I see a morbilliform eruption, usually what's on my mind is, 'Is this just a drug rash or is this DRESS?' "

Dr. Young said. DRESS often starts with a morbilliform eruption that is indistinguishable from a benign drug eruption.

"Timing is a major difference," she said. "If a patient develops a morbilliform drug eruption much later than I would expect, then my suspicion [for DRESS] goes up." Patients with DRESS often have fever and systemic symptoms. Proposed DRESS diagnostic criteria can be useful, but clinical judgment still plays a key role. If a patient does not satisfy diagnostic criteria but has some signs and is taking a drug that is associated with DRESS, "it is going to make me more suspicious and maybe make me recommend stopping that drug sooner," she said. Anticonvulsants such as carbamazepine, lamotrigine, and phenobarbital are among the drugs most commonly associated with DRESS.

Toxic erythemas

Patients may present with toxic erythemas, such as fixed drug reactions, erythema multiforme, SJS, and TEN. These drug reactions appear similar on biopsy but have different courses.

A patient with a fixed drug reaction often has a single lesion, and the lesion will occur in the same location every time the patient is exposed to the drug. Patients may develop additional lesions with subsequent exposures. These lesions typically are large, erythematous, well-demarcated plaques with central duskiness. "They can be bullous in the center, and they typically will heal with pigmentation, which is unique to this particular drug reaction," said Dr. Young. "When it gets more concerning and most important to differentiate is when you get generalized bullous fixed drug eruption." Generalized bullous fixed drug eruptions mimic and are difficult to clinically distinguish from TEN, which has a much poorer prognosis.

Toxic erythemas appear similar on biopsy, but have different courses

Patients with a fixed drug eruption are not as ill as patients with TEN and tend not to slough their skin to the extent seen with TEN. Interferon gamma, perforin, and Fas ligand have been implicated as mechanisms involved in fixed drug reactions. Unlike in TEN, regulatory T cells are abundant, which may explain why TEN and fixed drug reactions progress differently even though they appear to share pathologic mechanisms, Dr. Young said.

Erythema multiforme generally presents with classic target lesions and little mucosal involvement. Infections, most commonly herpes simplex virus (HSV) 1 and 2, may trigger erythema multiforme. Dr. Young recommends evaluating patients for HSV and checking serologies, even if patients have never had a herpes outbreak. "If you have no evidence for infection, you do have to consider discontinuing a medication," she said.

Stevens–Johnson syndrome and TEN

SJS and TEN are "the rarest of the severe cutaneous adverse drug reactions" and have "the highest morbidity and mortality," Dr. Young said. They appear to exist on a continuum where SJS may represent early TEN.

"This is a situation where you expect to see blistering of the skin [and] always mucosal involvement. You need to stop the drug immediately when you suspect this drug reaction," Dr. Young said.

One reason to distinguish SJS or early TEN from later TEN is that high-dose steroids may play a role in the treatment of SJS or early TEN. "Once you get past about 10% total body surface area, there is good evidence that steroids actually increase morbidity and mortality," she said.

If the eruption has occurred before, that factor suggests that a diagnosis of erythema multiforme or fixed drug reaction may be more likely than TEN.

An apparent lack of regulatory T cells in TEN could explain why patients with HIV infection are at much higher risk of developing SJS and TEN. Understanding the role that regulatory T cells play in severe drug eruptions may lead to new therapeutic options in the future, Dr. Young said.

Dr. Young had no disclosures. **NR**

—Jake Remaly

Researchers compare focused ultrasound and DBS for essential tremor

The techniques have similar efficacy, but their safety profiles and ability to manage disease progression differ.

LAS VEGAS—Focused ultrasound (FUS) thalamotomy and deep brain stimulation (DBS) of the ventral intermediate nucleus of the thalamus provide similar benefits for patients with essential tremor, according to two presentations delivered at the annual meeting of the North American Neuromodulation Society. The techniques' surgical procedures, associated risks, and adverse event profiles may influence neurologists and patients in their choice of treatment.

FUS allows neurosurgeons to apply thermal ablation to create a lesion on the thalamus. MRI guidance enables precise control of the lesion location (within approximately 1 mm) and of the treatment intensity. The surgery can be performed with high-resolution stereotactic framing.

DBS entails the surgical implantation of a neurostimulator and attached leads and electrodes. The neurosurgeon drills a hole of approximately 14 mm in diameter into the skull so that the electrode can be inserted stereotactically while the patient is awake or asleep. The neurostimulator is installed separately.

Both treatments provide functional benefits

In 2016, W. Jeff Elias, MD, director of stereotactic and functional neurosurgery at the University of Virginia in Charlottesville, and his colleagues published the results of a randomized controlled trial that compared FUS with sham treatment in 76 patients with essential tremor. At three months, hand tremor had improved by approximately 50% among treated patients, but controls had no significant benefit. The improvement among treated patients was maintained for 12 months. Disability and quality of life also improved after FUS.

A study by Schuurman et al. published in 2000 showed that DBS and FUS had similar efficacy at 1 year, said Kathryn L. Holloway, MD, professor of neurosurgery at Virginia Commonwealth University in Richmond. It included 45 patients with Parkinson's disease, 13 with essential tremor, and 10 with multiple sclerosis who were randomized 1:1 to FUS or DBS. The primary outcome was activities of daily living, and blinded physicians assessed patient videos. Most of the patients who improved had received DBS, and most of the ones who worsened had received FUS, said Dr. Holloway. Among patients with essential tremor, tremor improved by between 94% and 100% with either treatment.

To find more recent data about these treatments, Dr. Holloway searched the literature for studies of FUS or DBS for essential tremor. She analyzed only studies that included unselected populations, blinded evaluations within 1 or 2 years of surgery, and tremor scores for the treated side. She found two studies of FUS, including Dr. Elias's 2016 trial and a 2018 follow-up. Dr. Holloway also identified three trials of DBS.

In these studies, reduction of hand tremor was 55% with FUS and between 63% and 69% with DBS. Reduction of postural tremor was approximately 72% with FUS and approximately 67% with DBS. Reduction of action tremor was about 52% with FUS and between 65% and 71% with DBS. Overall, DBS appears to be more effective, said Dr. Holloway.

> **In a 2015 study that compared bilateral DBS, unilateral DBS, and unilateral FUS for essential tremor, the treatments provided similar benefits on hand tremor, disability, and quality of life.**

A 2015 study that compared bilateral DBS, unilateral DBS, and unilateral FUS for essential tremor indicated that the treatments provide similar benefits on hand tremor, disability, and quality of life, said Dr. Elias. FUS is inferior to DBS, however, for total tremor and axial tremor.

Furthermore, the efficacy of FUS wanes over time, said Dr. Elias. He and his colleagues conducted a pilot study of 15 patients with essential tremor who received FUS. At 6 years, 6 of 13 patients whose data were available still had a 50% improvement in tremor. "Some went on to [receive] DBS," said Dr. Elias. "Functional improvements persisted more than the tremor improvement."

W. Jeff Elias, MD

Kathryn L. Holloway, MD

Adverse events

In their 2016 trial of FUS, Dr. Elias and his colleagues observed 210 adverse events, which is approximately "what you would expect with a modern day, FDA-monitored clinical trial." Sensory effects and gait disturbance accounted for most of the thalamotomy-related adverse events. Sensory problems such as numbness or parestheisa persisted at 1 year in 14% of treated patients, and gait disturbance persisted at 1 year in 9%. The investigators did not observe any hemorrhages, infections, or cavitation-related effects from FUS.

In a 2018 analysis of five clinical trials of FUS for essential tremor, Fishman et al. found that 79% of adverse events were mild and 1% were severe. The risk of a severe adverse event therefore can be considered low, and it may decrease as neurosurgeons gain experience with the procedure, said Dr. Elias.

In the 2000 Schuurman et al. study, the researchers observed significantly fewer adverse events overall among patients with Parkinson's disease or essential tremor who received DBS, compared with patients who received FUS. Cognitive deterioration, severe dysarthria, and severe ataxia were more common in the FUS group than in the DBS group. Dr. Holloway's analysis of adverse events in the five more recent trials that she identified yielded similar results.

Although MRI-guided FUS is a precise way to make lesions, functional areas in the thalamus overlap, which makes it more difficult to target only the intended region, said Dr. Holloway. The functional overlap thus increases the risk of adverse events (e.g., sensory impairments, dysarthria, or ataxia). The adverse events that result from FUS may last as long as a year. "Patients will put up anything for about a month after surgery, and then they start to get annoyed," said Dr. Holloway.

In addition, Schuurman et al. found that FUS entailed a greater risk of permanent side effects, compared with DBS. "That's the key point here," said Dr. Holloway. Most of the adverse effects in the DBS group were resolved by adjusting or turning off the stimulator. Hardware issues resulting from DBS are frustrating, but reversible, but a patient with an adverse event after FUS often is "stuck with it," said Dr. Holloway. The Schuurman et al. data indicated that, in terms of adverse events, "thalamotomy was inferior to DBS," she added.

continued on next page

DBS may improve nonmotor symptoms in Parkinson's disease

Stimulation of the GPI, but not of the STN, is associated with improvement in sialorrhea and urinary function.

LAS VEGAS—Bilateral deep brain stimulation (DBS) of the globus pallidus internus (GPI) significantly improves genitourinary symptoms in patients with Parkinson's disease, according to a small study presented at the annual meeting of the North American Neuromodulation Society. DBS of the subthalamic nucleus (STN), however, does not significantly improve these symptoms.

"Further work will be needed to confirm whether DBS needs to be bilateral ... and whether demographic differences are significant," said Michael Gillogly, RN, clinical research nurse in the department of neurosurgery at Albany (New York) Medical Center. "The pilot data suggest that if all else is equal and the patient has significant urinary dysfunction as a major complaint, GPI DBS may be preferentially considered."

The benefits of DBS on motor symptoms in Parkinson's disease are well documented in the literature, but the technique's effects on nonmotor symptoms are less clear. Nonmotor symptoms—such as cognitive deficits, gastrointestinal dysfunction, genitourinary dysfunction, and sleep disturbance—are common in all stages of Parkinson's disease and significantly impair quality of life. Data indicate that speech and neuropsychological symptoms worsen with DBS of the STN, but research into the effect of DBS of the GPI on nonmotor symptoms is limited.

Mr. Gillogly and his colleagues considered all surgical candidates at their facility for enrollment into a study evaluating nonmotor outcomes in Parkinson's disease at baseline, before implantation, and at 6 months after DBS. Study outcomes were patient perception of urinary, swallowing, and gastrointestinal function at 6 months after DBS of the GPI, compared with DBS of the STN.

> Targeting of the subthalamic nucleus was not associated with improvements.

The researchers chose two tools each to measure sialorrhea, dysphagia, and genitourinary dysfunction. These tools included the Drooling Severity and Frequency Scale (DSFS), the Swallowing Disturbance Questionnaire, and the International Prostate Symptom Score (IPSS). The investigators also collected demographic information, including sex, age at the time of surgery, duration of illness, neuropsychological profile, and medication inventory.

Michael Gillogly, RN

In all, 34 patients (12 women) were enrolled in the study and completed each outcome measure preoperatively and at 6 months postoperatively. The mean age of the subjects at the time of surgery was 64 years. Eight received DBS of the GPI, and 26 received DBS of the STN. Mr. Gillogly and his colleagues observed a significant 31% improvement in DSFS score and a significant 24% improvement on the IPSS among GPI-targeted patients. They found no significant improvements among patients who had STN targeting. When the investigators compared patients with unilateral lead placement and those with bilateral lead placement, they observed that all of the significant improvement among patients with GPI targeting occurred when treatment was bilateral.

The small sample size is a notable limitation of the study, and subset analyses were limited, said Mr. Gillogly. In addition, it was difficult to determine whether the symptoms studied were directly related to Parkinson's disease, because they often arise as part of the natural aging process. "Other limitations of the study include lack of objective measurements, as these are all patient perception, and the innate limitations of self-reported questionnaires," said Mr. Gillogly.

Two of the researchers reported having consulted for Medtronic, which markets a DBS system. One author received grant funding and consulting fees from Boston Scientific, Medtronic, and Abbott, all of which make DBS devices. **NR**

—Erik Greb

FUS entails a greater risk of permanent side effects than does DBS.

continued

Implantation of DBS entails the risks inherent to surgeries that open the skull (such as seizures, air embolism, and hemorrhage). DBS entails a 2% risk of hemorrhage or infection, said Dr. Elias. Furthermore, as much as 15% of patients who undergo DBS implantation require additional surgery.

"FUS is not going to cause a life-threatening hemorrhage, but DBS certainly can," said Dr. Holloway.

Managing disease progression

Essential tremor is a progressive disease, and older patients are more likely to have exponential progression than linear progression. Data such as those published by Zhang et al. indicate that DBS can "keep up with the progression of the disease," said Dr. Holloway. The authors found that tremor scores did not change significantly over approximately 5 years when patients with essential tremor who had received DBS implantation had periodic assessments and increases in stimulation parameters when appropriate.

If a patient with essential tremor undergoes FUS thalamotomy and has subsequent disease progression, DBS may be considered for reducing tremor, said Dr. Holloway. Most adverse events resulting from DBS implantation are reversible with adjustment of the stimulation parameters. A second thalamotomy, however, could cause severe dysarthria and other irreversible adverse events. "Only DBS can safely address tremor progression," said Dr. Holloway. **NR**

—Erik Greb

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Vaccination and antiviral treatment do not affect stroke risk following shingles

Preventing shingles through vaccination might be the best method for preventing shingles-associated acute ischemic stroke.

HONOLULU—Vaccination against shingles or treating shingles with antiviral medication once it occurs does not alter the increased risk of acute ischemic stroke attributed to reactivated herpes zoster virus, according to findings from a retrospective study of Medicare beneficiaries with shingles and ischemic stroke.

The findings suggest that primary prevention of shingles through vaccination might be the most effective approach to prevent shingles-associated acute ischemic stroke, said the researchers, who presented the study at the International Stroke Conference sponsored by the American Heart Association.

Almost one in three people in the United States will develop shingles, also known as herpes zoster, in their lifetime, according to the Centers for Disease Control and Prevention. Previous research has not simultaneously examined the effect of shingles vaccination and antiviral treatment following shingles onset on the risk of acute ischemic stroke.

Quanhe Yang, PhD, a senior scientist at the CDC, and his colleagues examined data for 35,186 Medicare fee-for-service beneficiaries who were 66 years or older, diagnosed with shingles during 2008-2014, and diagnosed with acute ischemic stroke within a year of shingles diagnosis. Using a self-controlled case series design, the investigators analyzed the association between shingles and stroke. Dr. Yang and his colleagues estimated the incident rate ratio (IRR) by comparing the incidence of stroke during risk periods (i.e., periods following shingles), compared with control periods. To minimize confounding by age, they restricted their analyses to approximately 365 days from the shingles index date.

To investigate how vaccination against shingles with Zostavax and antiviral treatment following shingles affected stroke risk, the researchers classified beneficiaries into the following four groups: Group 1 had no vaccination and no antiviral treatment (49% of beneficiaries), Group 2 had vaccination only (9%), Group 3 had antiviral treatment only (34%), and Group 4 had vaccination and antiviral treatment (8%). The researchers tested for interaction to examine the changes in IRRs across the four groups.

IRRs for stroke progressively declined as time passed from the index shingles date, from 1.61 at 0-14 days following shingles to 1.35 at 15-30 days, 1.16 at 31-90 days, and 1.05 at 91-180 days. The researchers found no evidence that shingles vaccination and antiviral treatment modified the risk of acute ischemic stroke. The association between shingles and risk for acute ischemic stroke was consistent across age groups (i.e., 66-74 years, 75-84 years, and 85 years or older), sex, and race (i.e., non-Hispanic white, non-Hispanic black, and Hispanic, other).

One of the study's strengths was that its sample was a large national cohort of Medicare fee-for-service beneficiaries, Dr. Yang said. In addition, the study design eliminated all fixed confounding effects. Potential weaknesses, however, included the fact that herpes zoster diagnosis was based on administrative data and that the vaccine's efficacy declines over time.

The findings suggest that the importance of following the recommended shingles vaccination protocol in the prevention of shingles, Dr. Yang said. Shingrix, a vaccine that the Food and Drug Administration approved in 2017, prevents shingles with an efficacy greater than 90%, he added.

The investigators reported no funding source or disclosures for this study.

NR

—Erik Greb

Obesity paradox applies to post-stroke mortality

Overweight and obese VA stroke patients have lower 30-day and 1-year all-cause mortality after an in-hospital stroke.

CHICAGO—Overweight and obese military veterans who experienced an in-hospital stroke had a lower 30-day and 1-year all-cause mortality than did those who were normal weight in a large national study, Lauren Costa reported at the American Heart Association scientific sessions.

Underweight patients had a significantly increased mortality risk, added Ms. Costa of the VA Boston Healthcare System.

It's yet another instance of what is known as the obesity paradox, which has also been described in patients with heart failure, acute coronary syndrome, MI, chronic obstructive pulmonary disease, and other conditions.

Ms. Costa presented a retrospective study of 26,267 patients in the Veterans Health Administration database who had a first stroke in hospital during 2002-2012. There were subsequently 14,166 deaths, including 2,473 within the first 30 days and 5,854 in the first year post stroke.

Each patient's body mass index was calculated based on the average of all BMI measurements obtained 1-24 months prior to the stroke. The analysis of the relationship between BMI and poststroke mortality included extensive statistical adjustment for potential confounders, including age, sex, smoking, cancer, dementia, peripheral artery disease, diabetes, coronary heart disease, atrial fibrillation, chronic kidney disease, use of statins, and antihypertensive therapy.

Classifying the study participants into eight BMI categories, Ms. Costa found that the adjusted risk of 30-day all-cause mortality post stroke was reduced by 22% to 38% in patients in the overweight or obese groupings, compared with the reference population with a normal-weight BMI of 22.5 to less than 25 kg/m_2. One-year, all-cause mortality showed the same pattern of BMI-based significant differences.

Of deaths within 30 days post stroke, 34% were stroke-related. In an analysis restricted to that group, the evidence of an obesity paradox was attenuated. Indeed, the only BMI group with an adjusted 30-day stroke-related mortality significantly different from the normal-weight reference group were patients with Class III obesity, defined as a BMI of 40 or more. Their risk was reduced by 45%.

The obesity paradox remains controversial among epidemiologists. The increased mortality associated with being underweight among patients with diseases where the obesity paradox has been documented is widely thought to be caused by frailty or an underlying illness not adjusted for in analyses. But the mechanism for the reduced mortality risk in overweight and obese patients seen in the VA stroke study and other studies remains unknown.

Ms. Costa reported having no financial conflicts regarding her study, which was supported by the Department of Veterans Affairs.

NR

—Bruce Jancin

Novel plasma biomarkers may predict preclinical Alzheimer's disease

The approach will need to be validated and translated "to a simpler automated platform suitable for wider utility."

A plasma proteomic study has identified new biomarkers of Alzheimer's disease pathology in cognitively unimpaired individuals, researchers reported in *Science Advances*.

"To our knowledge, this is the first time that a multianalyte plasma biomarker panel for an Alzheimer's disease–related phenotype has been found and independently replicated by a nontargeted mass spectrometry approach," said Nicholas J. Ashton, PhD, of King's College London and the University of Gothenburg in Sweden, and his research colleagues.

> **Evidence suggests that cerebrovascular disease plays a role in Alzheimer's disease and that amyloid-beta may be involved in thrombosis, fibrinolysis, and inflammation.**

Biomarkers could aid clinical trials

Blood-based measures that predict amyloid-beta burden in preclinical Alzheimer's disease have the potential to help investigators conduct clinical trials and aid in diagnostic management. However, this novel approach needs to be validated and translated "to a simpler automated platform suitable for wider utility," the investigators noted. In addition, it is unclear whether their classifier can track changes in amyloid-beta or differentiate between other diseases with amyloid-beta pathology.

Advances in mass spectrometry technology have renewed interest in the analysis of plasma proteins in patients with various diseases. To assess whether proteomic discovery in plasma can help predict amyloid-beta burden in preclinical Alzheimer's disease, Dr. Ashton and his colleagues studied 238 cognitively unimpaired individuals from the Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing (AIBL) and the Kerr Anglican Retirement Village Initiative in Ageing Health (KARVIAH). The participants had undergone PET to determine their amyloid-beta status. In the AIBL cohort (n = 144), 100 participants were amyloid-beta negative, and 44 were amyloid-beta positive. In the KARVIAH cohort (n = 94), 59 participants were amyloid-beta negative, and 35 were amyloid-beta positive. There were significantly more *APOE4* carriers in the amyloid-beta–positive groups than in the amyloid-beta–negative groups. In addition, the amyloid-beta–positive groups tended to be older.

A support vector machine analysis created classifiers predicting amyloid-beta positivity in the AIBL cohort using demographics, proteins, or both. The researchers then tested each classifier in the KARVIAH dataset to identify which model best predicted amyloid-beta positivity. The optimal model included 10 protein features (prothrombin, adhesion G protein–coupled receptor, amyloid-beta A4 protein, NGN2, DNAH10, REST, NfL, RPS6KA3, GPSM2, FHAD1) and two demographic features (*APOE4* count and age).

Amyloid beta may affect thrombosis

The classifier achieved a testing area under the receiver operator characteristic curve of 0.891 in the KARVIAH cohort to predict amyloid-beta positivity in cognitively unimpaired individuals with a sensitivity of 0.78 and specificity of 0.77.

The 10 protein features "represent a diverse array of pathways," and the highest ranked feature was the serine protease prothrombin, which is a precursor to thrombin, the authors noted. "Multiple lines of evidence support that cerebrovascular disease may play a role in Alzheimer's disease and that amyloid-beta may be involved in thrombosis, fibrinolysis, and inflammation via its interaction with the coagulation cascade," the researchers wrote.

The role of neurofilament light

Two of the biomarkers, amyloid-beta A4 protein and neurofilament light, have been examined in prior research and had a greater effect size in a secondary analysis that included participants with mild cognitive impairment and Alzheimer's disease. This finding confirms "their connection with the more established disease state," Dr. Ashton and colleagues said. In the secondary analysis, the optimal classifier included one demographic factor (*APOE4* count) and nine protein features, eight of which also were used in the cognitively unimpaired classifier.

The study was funded in part by the National Institute for Health Research Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, and many authors reported additional research support from various institutions. One author is an employee of Johnson & Johnson and a named inventor on unrelated biomarker intellectual property owned by Proteome Science and King's College London.

NR

–Jake Remaly

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Does adherence to a Mediterranean diet reduce the risk of Parkinson's disease?

Greater adherence to a Mediterranean diet is associated with lower probability of prodromal Parkinson's disease, but questions about this relationship remain.

Among older adults, adherence to a Mediterranean diet is associated with lower probability of prodromal Parkinson's disease, according to research published in *Movement Disorders*.

"Recommending the Mediterranean diet pattern, either to reduce the risk or lessen the effects ... of prodromal Parkinson's disease, needs to be considered and further explored," said lead author Maria I. Maraki, PhD, of the department of nutrition and dietetics at Harokopio University in Athens, Greece, and her research colleagues.

Evidence regarding the effect of a Mediterranean diet on Parkinson's disease risk remains limited, however, and physicians should be cautious in interpreting the data, researchers noted in accompanying editorials.

"There is a puzzling constellation of information and data that cannot be reconciled with a simple model accounting for the role of diet, vascular risk factors, and the neurodegenerative process and mechanisms underlying Parkinson's disease," Connie Marras, MD, PhD, and Jose A. Obeso, MD, PhD, said in an editorial. Given Maraki et al.'s findings, "most of us would be glad to accept that such a causal inverse association exists and can therefore be strongly recommended to our patients," but "further work is needed before definitive conclusions can be reached," Dr. Marras and Dr. Obeso wrote. Dr. Marras is affiliated with the University Health Network and the University of Toronto. Dr. Obeso is affiliated with University Hospital HM Puerta del Sur, CEU San Pablo University, Móstoles, Spain.

The role of diet

Prior research has suggested that adherence to the Mediterranean diet—characterized by consumption of nonrefined cereals, fruits, vegetables, legumes, potatoes, fish, and olive oil—may be associated with reduced risk of Parkinson's disease. In addition, studies have found that adherence to the Mediterranean diet may be protective in other diseases, including dementia and cardiovascular disease. Dr. Maraki and her colleagues sought to assess whether adherence to the Mediterranean diet is associated with the likelihood of prodromal Parkinson's disease or its manifestations. To calculate the probability of prodromal Parkinson's disease, the investigators used a tool created by the International Parkinson and Movement Disorder Society (MDS) that takes into account baseline risk factors as well as prodromal markers such as constipation and motor slowing.

They analyzed data from 1,731 participants in the population-based Hellenic Longitudinal Investigation of Aging and Diet (HELIAD) cohort in Greece. Participants, 41% of whom were male, were aged 65 years or older and did not have Parkinson's disease. They completed a detailed food frequency questionnaire, and the researchers calculated how closely each participant's diet adhered to the Mediterranean diet. Diet adherence scores ranged from 0 to 55, with higher scores indicating greater adherence.

The median probability of prodromal Parkinson's disease was 1.9% (range, 0.2%–96.7%), and the probability was lower among those with greater adherence to the Mediterranean diet. This difference was "driven mostly by nonmotor markers of prodromal Parkinson's disease," including depression, constipation, urinary dysfunction, and daytime somnolence, the researchers said. "Each unit increase in Mediterranean diet score was associated with a 2% decreased probability for prodromal Parkinson's disease." Compared with participants in the lowest quartile of Mediterranean diet adherence, those in the highest quartile had an approximately 21% lower probability for prodromal Parkinson's disease.

Potential confounding

"This study pushes the prodromal criteria into performing a job they were never designed to do," which presents potential pitfalls, Ronald B. Postuma, MD, of the department of neurology at Montreal General Hospital in Quebec, said in an accompanying editorial.

While the MDS criteria were designed to assess the likelihood that any person over age 50 years is in a state of prodromal Parkinson's disease, the present study aimed to evaluate whether a single putative risk factor for Parkinson's disease is associated with the likelihood of its prodromal state.

In addition, the analysis did not include some of the prodromal markers that are part of the MDS criteria, including olfaction, polysomnographic-proven REM sleep behavior disorder, and dopaminergic functional neuroimaging.

"As pointed out by the researchers, many of the risk factors in the prodromal criteria are potentially confounded by factors other than Parkinson's disease; for example, one could imagine that older people, men, or farmers (with their higher pesticide exposure) are less likely to follow the Mediterranean diet simply because of different cultural lifestyle patterns," Dr. Postuma said.

It is also possible that the Mediterranean diet affects prodromal markers such as constipation, sleep, or depression without affecting underlying neurodegenerative disease. In any case, the effect sizes observed in the study were small, and there was no evidence that participants who adhered most closely to a Mediterranean diet had less parkinsonism, Dr. Postuma said.

These limitations do not preclude physicians from recommending the diet for other reasons. "Numerous studies, reviews, meta-analyses, and randomized controlled trials consistently rank the Mediterranean diet as among the healthiest diets available," Dr. Postuma said. "So, one can clearly recommend diets such as these, even if not necessarily for Parkinson's disease prevention."

Adding insights

The researchers used a Mediterranean diet score that was developed in a population of adults from metropolitan Athens, "an area not unlike the one in which the score is being applied in the HELIAD study," Christy C. Tangney, PhD, professor of clinical nutrition and preventive medicine and associate dean for research at Rush University Medical Center, Chicago, said in a separate editorial. As expected, the average Mediterranean diet adherence score in this study was higher than that in the Chicago Health and Aging Project (33.2 vs. 28.2).

"If we can identify differences in diet or lifestyle patterns and risk of this latent phase of Parkinson's disease neurodegeneration, we may be one step closer to identifying preventive measures," she said. Follow-up reports from HELIAD and other cohorts may allow researchers to assess how changes in dietary patterns relate to changes in Parkinson's disease markers, the probability of prodromal Parkinson's disease, and incident Parkinson's disease, Dr. Tangney said.

The study authors had no conflicts of interest or financial disclosures. The study was supported by a grant from the Alzheimer's Association, an ESPA-EU grant cofunded by the European Social Fund and Greek National resources, and a grant from the Ministry for Health and Social Solidarity (Greece). Dr. Maraki and a coauthor have received financial support from the Greek State Scholarships Foundation. Dr. Tangney and Dr. Postuma had no conflicts of interest. **NR**

—Jake Remaly

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International survey probes oxygen's efficacy for cluster headache

Oxygen is a highly effective therapy with few complications, patients report.

Oxygen is a highly effective treatment for cluster headache with few complications, according to patient survey results published in the February issue of *Headache*. According to the results, triptans also are highly effective, with some side effects. Newer medications deserve further study, the researchers said.

To assess the effectiveness and adverse effects of acute cluster headache medications in a large international sample, Stuart M. Pearson, a researcher in the department of psychology at the University of West Georgia in Carrollton, and his coauthors analyzed data from the Cluster Headache Questionnaire. Respondents from more than 50 countries completed the online survey; most were from the United States, the United Kingdom, and Canada. The survey included questions about cluster headache diagnostic criteria and medication effectiveness, complications, and access to medications.

In all, 3,251 subjects participated in the questionnaire, and 2,193 respondents met criteria for the study; 1,604 had cluster headache, and 589 had probable cluster headache. Among the respondents with cluster headache, 68.8% were male, 78.0% had episodic cluster headache, and the average age was 46 years. More than half of respondents reported complete or very effective treatment for triptans (54%) and oxygen (also 54%). The proportions of respondents who reported that ergot derivatives, caffeine or energy drinks, and intranasal ketamine were completely or very effective ranged from 14% to 25%. Patients were less likely to report high levels of efficacy for opioids (6%), intranasal capsaicin (5%), and intranasal lidocaine (2%).

Participants experienced few complications from oxygen, with 99% reporting no or minimal physical and medical complications, and 97% reporting no or minimal psychological and emotional complications. Patients also reported few complications from intranasal lidocaine, intranasal capsaicin, and caffeine and energy drinks. For triptans, 74% of respondents reported no or minimal physical and medical complications, and 85% reported no or minimal psychological and emotional complications.

> "Oxygen in particular had a high rate of complete effectiveness, a low rate of ineffectiveness, and a low rate of physical, medical, emotional, and psychological side effects."

Among the 139 participants with cluster headache who were aged 65 years or older, responses were similar to those for the entire population. In addition, the 589 respondents with probable cluster headache reported similar efficacy data, compared with respondents with a full diagnosis of cluster headache.

"Oxygen in particular had a high rate of complete effectiveness, a low rate of ineffectiveness, and a low rate of physical, medical, emotional, and psychological side effects," the investigators said. "However, respondents reported that it was difficult to obtain."

Limited insurance coverage of oxygen may affect access, even though the treatment has a Level A recommendation for the acute treatment of cluster headache in the American Headache Society guidelines, the authors said. Physicians also may pose a barrier. A prior study found that 12% of providers did not prescribe oxygen for cluster headache because they doubted its efficacy or did not know about it. In addition, there may be safety concerns about using flammable gas in a patient population that has high rates of smoking, the researchers said.

Limitations of the study include the survey's use of nonvalidated questions, the lack of a formal clinical diagnosis of cluster headache, and the grouping of all triptans, rather than assessing individual triptan medications, such as sumatriptan subcutaneous, alone.

The study received funding from Autonomic Technologies and Clusterbusters. One of the authors has served as a paid consultant to Eli Lilly as a member of the data monitoring committee for clinical trials of galcanezumab for cluster headache and migraine. **NR**

—Jake Remaly

Suggested Reading

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MENTALFLOSS

Brain surgery may be a laughing matter

Electrical stimulation of a focal pathway in the brain causes immediate laughter, followed by a sense of calm and happiness, even during awake brain surgery, according to research published online ahead of print Feb. 11 in the *Journal of Clinical Investigation*. Investigators at Emory University School of Medicine in Atlanta observed these effects of stimulation in a patient with epilepsy who was undergoing diagnostic monitoring for seizure diagnosis. They took advantage of these effects to help her complete a separate awake brain surgery two days later.

The researchers confirmed the behavioral effects of direct electrical stimulation of the cingulum bundle, a white matter tract in the brain, in two other epilepsy patients undergoing diagnostic monitoring.

The technique is a "potentially transformative" way to calm patients during awake brain surgery, even for people who are not especially anxious, said the investigators. For optimal protection of critical brain functions during surgery, patients may need to be awake, rather than sedated, so that doctors can talk with them, assess their language skills, and detect impairments that may arise from the resection.

"Even well-prepared patients may panic during awake surgery, which can be dangerous," says lead author Kelly Bijanki, PhD, assistant professor of neurosurgery at the university. "This particular patient was especially prone to it because of moderate baseline anxiety. And upon waking from global anesthesia, she did indeed begin to panic. When we turned on her cingulum stimulation, she immediately reported feeling happy and relaxed, told jokes about her family, and was able to tolerate the awake procedure successfully."

In addition to its application during awake surgery, an understanding of how cingulum bundle stimulation works could also inform efforts to better treat depression, anxiety disorders, or chronic pain using deep brain stimulation. Previous investigators have reported that direct electrical stimulation of other parts of the brain can trigger laughter, but this study demonstrates that cingulum bundle stimulation provides meaningful clinical benefits.

Bijanki KR, Manns JR, Inman CS, et al. Cingulum stimulation enhances positive affect and anxiolysis to facilitate awake craniotomy. *J Clin Invest*. 2019 Feb 11 [Epub ahead of print].

Age of migraine onset may affect stroke risk

Onset of migraine with aura before age 50 is not associated with ischemic stroke, an analysis finds.

The age at which a patient develops migraine with aura may be an important factor in assessing stroke risk, according to a prospective cohort study published in *Headache*.

Patients who had onset of migraine with visual aura after age 50 years had an increased risk of ischemic stroke, compared with patients with no headache, the researchers found. Patients with longer exposure to migraine with visual aura—that is, onset before age 50 years—did not have significantly increased ischemic stroke risk, said X. Michelle Androulakis, MD, of the department of neurology at the University of South Carolina in Columbia, and her colleagues.

"Migraine, especially migraine with aura, is associated with increased risk of ischemic stroke," but whether age of migraine onset affects the risk of cardiovascular disease has been unclear, the researchers said.

To examine the risk of ischemic stroke in migraineurs with and without aura with onset before and after age 50 years, the investigators conducted a post hoc analysis of data from the ongoing Atherosclerosis Risk in Communities (ARIC) study. The researchers adjusted for potential confounders, including diabetes, body mass index, hypertension, and hyperlipidemia.

In ARIC, participants completed a questionnaire about their migraine history at their third study visit (1993–1995) and were followed for ischemic stroke incidence over 20 years.

Of the 11,592 ARIC participants included in the analysis (mean age, 61 years; 76.5% white; and 55.3% female), 447 had migraine with aura, and 1,128 had migraine without aura. Onset of migraine with aura at age 50 years or older (average duration, 4.75 years) was associated with more than twofold greater risk of ischemic stroke, compared with no headache (multivariable adjusted hazard ratio = 2.17). Onset of migraine with aura before age 50 years (average duration, 28.17 years) was not significantly associated with stroke. A logistic regression model yielded consistent results.

In addition, patients with migraine without aura did not have an increased risk of stroke, regardless of the age of onset. The absolute risk for stroke in migraine with aura was 8.27%, and the absolute risk in migraine without aura was 4.25%.

"We found unexpected results suggesting that the onset of migraine with aura before age 50 is not associated with ischemic stroke.... These results are specific to first-time ischemic stroke incidents that occurred in mid- to late life; therefore, it cannot be generalized to stroke in younger patients," the authors wrote.

It could be that migraine with aura symptoms that start at a later age are a red flag for paradoxical emboli from a patent foramen ovale or microemboli, Dr. Androulakis and her colleagues noted. It also is possible that the degree of cortical spreading depression required to induce migraine with aura symptoms is different later in life versus earlier in life.

"This study underscores the importance of [migraine with aura] symptoms onset in evaluation of ischemic stroke risk in late life," the researchers concluded.

The authors had no relevant conflicts of interest. ARIC has been funded by the National Heart, Lung, and Blood Institute. **NR**

—Jake Remaly

Suggested Reading

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Tic disorders are associated with obesity and diabetes

Patients with Tourette syndrome or chronic tic disorder have a higher risk for metabolic and cardiovascular health problems.

Tourette syndrome and chronic tic disorder are associated with a "substantial risk" of metabolic and cardiovascular disorders such as obesity, type 2 diabetes mellitus, and circulatory system diseases, according to a study published online ahead of print Jan. 14 in *JAMA Neurology*.

The movement disorders are associated with cardiometabolic problems "even after taking into account a number of covariates and shared familial confounders and excluding relevant psychiatric comorbidities," the researchers wrote. "The results highlight the importance of carefully monitoring cardiometabolic health in patients with Tourette syndrome or chronic tic disorder across the lifespan, particularly in those with comorbid attention-deficit/hyperactivity disorder (ADHD)."

Gustaf Brander, a researcher in the department of clinical neuroscience at Karolinska Institutet in Stockholm, and his colleagues conducted a longitudinal population-based cohort study of individuals living in Sweden between Jan. 1, 1973, and Dec. 31, 2013. The researchers assessed outcomes for patients with previously validated diagnoses of Tourette syndrome or chronic tic disorder in the Swedish National Patient Register. Main outcomes included obesity, dyslipidemia, hypertension, type 2 diabetes mellitus, and cardiovascular diseases, including ischemic heart diseases, arrhythmia, cerebrovascular diseases, transient ischemic attack, and arteriosclerosis. In addition, the researchers identified families with full siblings discordant for Tourette syndrome or chronic tic disorder.

Of the more than 14 million individuals in the cohort, 7,804 (76.4% male; median age at first diagnosis, 13.3 years) had a diagnosis of Tourette syndrome or chronic tic disorder in specialist care. Furthermore, the cohort included 5,141 families with full siblings who were discordant for these disorders.

Individuals with Tourette syndrome or chronic tic disorder had a higher risk for any metabolic or cardiovascular disorder, compared with the general population (hazard ratio adjusted by sex and birth year [aHR], 1.99) and sibling controls (aHR, 1.37). Specifically, individuals with Tourette syndrome or chronic tic disorder had higher risks for obesity (aHR, 2.76), type 2 diabetes mellitus (aHR, 1.67), and circulatory system diseases (aHR, 1.76).

The increased risk of any cardiometabolic disorder was significantly greater for males than it was for females (aHRs, 2.13 vs. 1.79), as was the risk of obesity (aHRs, 3.24 vs. 1.97).

The increased risk for cardiometabolic disorders in this patient population was evident by age 8 years. Exclusion of those patients with comorbid ADHD reduced but did not eliminate the risk (aHR, 1.52). The exclusion of other comorbidities did not significantly affect the results. Among patients with Tourette syndrome or chronic tic disorder, those who had received antipsychotic treatment for more than 1 year were significantly less likely to have metabolic and cardiovascular disorders, compared with patients not taking antipsychotic medication. This association may be related to "greater medical vigilance" and "should not be taken as evidence that antipsychotics are free from cardiometabolic adverse effects," the authors noted.

The study was supported by a research grant from Tourettes Action. In addition, authors reported support from the Swedish Research Council and a Karolinska Institutet PhD stipend. Two authors disclosed personal fees from publishers; one author disclosed grants and other funding from Shire. **NR**

—Jake Remaly

Suggested Reading

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Clinical benefits persist 5 years after thymectomy for myasthenia gravis

Patients with generalized nonthymomatous myasthenia gravis who undergo thymectomy may have better long-term clinical outcomes and require less prednisone.

Thymectomy may continue to benefit patients with myasthenia gravis 5 years after the procedure, according to an extension study published in *Lancet Neurology*. Patients with generalized nonthymomatous myasthenia gravis who underwent thymectomy had better long-term clinical outcomes and required less prednisone, compared with patients who received prednisone alone.

The study evaluated the clinical status, medication requirements, and adverse events of patients with myasthenia gravis who completed a randomized controlled trial of thymectomy plus prednisone versus prednisone alone and agreed to participate in a rater-blinded 2-year extension.

> Significantly more patients who underwent thymectomy had no functional limitations from the disease at 5 years, compared with patients who did not.

"Thymectomy within the first few years of the disease course in addition to prednisone therapy confers benefits that persist for 5 years ... in patients with generalized nonthymomatous myasthenia gravis," said lead study author Gil I. Wolfe, MD, chair of the department of neurology at the University at Buffalo in New York, and his research colleagues. "Results from the extension study provide further support for the use of thymectomy in management of myasthenia gravis and should encourage serious consideration of this treatment option in discussions between clinicians and their patients," they wrote. "Our results should lead to revision of clinical guidelines in favor of thymectomy and could potentially reverse downward trends in the use of thymectomy in overall management of myasthenia gravis."

The main 3-year results of the Thymectomy Trial in Nonthymomatous Myasthenia Gravis Patients Receiving Prednisone (MGTX) were reported in 2016; the international trial found that thymectomy plus prednisone was superior to prednisone alone at 3 years. The extension study aimed to assess the durability of the treatment response.

MGTX enrolled patients aged 18-65 years who had generalized nonthymomatous myasthenia gravis of less than 5 years' duration and Myasthenia Gravis Foundation of America Clinical Classification Class II–IV disease. Of 111 patients who completed MGTX, 68 entered the extension study, and 50 completed the 60-month assessment (24 patients in the prednisone alone group and 26 patients in the prednisone plus thymectomy group).

At 5 years, patients in the thymectomy plus prednisone group had significantly lower time-weighted average Quantitative Myasthenia Gravis (QMG) scores (5.47 vs. 9.34) and mean alternate-day prednisone doses (24 mg vs. 48 mg), compared with patients who received prednisone alone. Twelve of 35 patients in the thymectomy group and 14 of 33 patients in the prednisone group had at least one adverse event by month 60. No treatment-related deaths occurred in the extension phase.

At 5 years, significantly more patients who underwent thymectomy had minimal manifestation status (i.e., no functional limitations from the disease other than some muscle weakness)—88% versus 58%. The corresponding figures at 3 years were 67% and 47%.

In addition, 3-year and 5-year data indicate that the need for hospitalization is reduced after surgery, compared with medical therapy alone, Dr. Wolfe said.

Gil I. Wolfe, MD

Two patients in each treatment arm had an increase of 2 points or more in the QMG score, indicating clinical worsening.

"Our current findings reinforce the benefit of thymectomy seen in [MGTX], dispelling doubts about the procedure's benefits and how long those benefits last," said Dr. Wolfe. "We do hope that the new findings help reverse the apparent reluctance to do thymectomy and that the proportion of patients with myasthenia gravis who undergo thymectomy will increase."

The authors noted that the small sample size of the extension study may limit its generalizability.

The study received funding from the National Institutes of Health. Dr. Wolfe reported grants from the NIH, the Muscular Dystrophy Association, the Myasthenia Gravis Foundation of America, CSL-Behring, and ArgenX, as well as personal fees from Grifols, Shire, and Alexion Pharmaceuticals. Coauthors reported working with and receiving funds from agencies, foundations, and pharmaceutical companies. **NR**

—Jake Remaly

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Statins cut vascular events in elderly patients

Analysis challenges current practice of discontinuation after age 75 years.

Statin therapy appears to reduce the risk of major vascular events for patients of all age groups, but there is less evidence that older patients with evidence of occlusive vascular disease benefit from the treatment, according to a recent meta-analysis of 28 trials from the Cholesterol Treatment Trialists' Collaboration published February 2 in the *Lancet*.

Statins are "useful and affordable drug[s] that reduce heart attacks and strokes in older patients. Until now, there has been an evidence gap, and we wanted to look at their efficacy and safety in older people," Jordan Fulcher, BSc (Med), MBBS, from the Cholesterol Treatment Trialists' (CTT) Collaboration and the University of Sydney stated in a press release. "Our analysis indicates that major cardiovascular events were reduced by about a fifth, per mmol/L lower LDL cholesterol, by statin therapy across all age groups. Despite previous concerns, we found no adverse effect on cancer or nonvascular mortality in any age group."

Significant reduction in major vascular events

The researchers examined 186,854 participants from 28 CTT trials undergoing statin therapy, of whom 14,483 (8%) were older than 75. Patients were divided into six groups based on age, and researchers examined the risk of major cardiovascular events such as stroke, coronary revascularization and major coronary events, as well as the incidence of cancer and vascular mortality.

Among all age groups, there was a significant reduction in major vascular events, with a 21% proportional reduction per 1.0-mmol/L reduction in LDL cholesterol (risk ratio, 0.79; 95% confidence interval, 0.77–0.81) among patients receiving statin therapy or a more intensive statin regimen, and there was a 24% proportional reduction (RR, 0.76; 95% CI, 0.73–0.79) of major coronary events per 1.0-mmol/L reduction in LDL cholesterol, with older age resulting in a lower proportional reduction of major coronary events (P = .009). The researchers also found a proportional reduction of coronary revascularization procedures by 25% (RR, 0.75; 95% CI, 0.73–0.78) and stroke by 16% (RR, 0.84; 95% CI, 0.80–0.89) among patients of any age group receiving statin therapy or more intensive statin regimen, with no significant differences between age groups.

There was a 12% proportional reduction in vascular mortality per 1.0-mmol/L reduction in LDL cholesterol (RR, 0.88; 95% CI, 0.85–0.91), but this statistic did not remain significant after the researchers excluded four trials that included patients with heart failure or who were receiving renal dialysis. After excluding these trials from the overall analysis, the researchers found the smaller proportional reductions persisted for older patients for major coronary events (P = .01) but was no longer significant for major vascular events.

The researchers noted that their study was limited by the highly selected patient population, the low percentage of patients older than 75 years, inclusion of trials that may not have recorded some nonserious adverse events, and not including some trials that were not part of the CTT.

This study was funded by Australian National Health and Medical Research Council, National Institute for Health Research Oxford Biomedical Research Centre, UK Medical Research Council, and British Heart Foundation. The authors have reported personal fees, grants, and consulting fees from Abbott, Aegerion, Amgen, Arisaph, AstraZeneca, Bayer, Beckmann, Berlin-Chemie, Boehringer Ingelheim, Daiichi Sankyo, Dalcor, DuPont, Esperion, GlaxoSmithKline, ISIS Pharmaceuticals, Kowa, Mylan, Pfizer, Roche, Sanofi, Singulex, The Medicines Company, and Vatera Capital, as well as the British Heart Foundation, Cancer Research UK, National Institute for Health Research Oxford Biomedical Research Centre, Medical Research Council, Nuffield Department of Population Health, Weill Cornell Medicine, and UK Biobank.

Statin therapy should be considered for patients older than 75

Statin therapy is often discontinued for older patients who have concomitant disease or other considerations, but it should still be considered in older patients when the benefits outweigh the risks, Bernard M.Y. Cheung, PhD, and Karen S.L. Lam, MD, wrote in a related editorial. Drs. Cheung and Lam are from the department of medicine at Queen Mary Hospital, University of Hong Kong in Hong Kong Special Administrative Region, China.

"Even if the relative risk reduction in people older than 75 is less than expected, statin therapy might still be justified by a high baseline cardiovascular risk, which is usually present in older people," they said.

One explanation for the decreased relative risk reduction among older patients from the results by Fulcher et al. in the CTT Collaboration trial could have been the inclusion of older patients with cardiac and renal failure, and treating patients with lower cardiac risk or lowering LDL cholesterol in patients at risk of cardiovascular events can help prevent major vascular events later.

Ultimately, no drug is harmless and the risk and benefits must be weighed before making a decision to use statins with older patients just as they would in any other patient population. "The challenge for the health care profession and the media is to convey risks and benefits in ways that patients can understand, enabling them to make an informed choice," Drs. Cheung and Lam wrote. **NR**

—Jeff Craven

Suggested Reading

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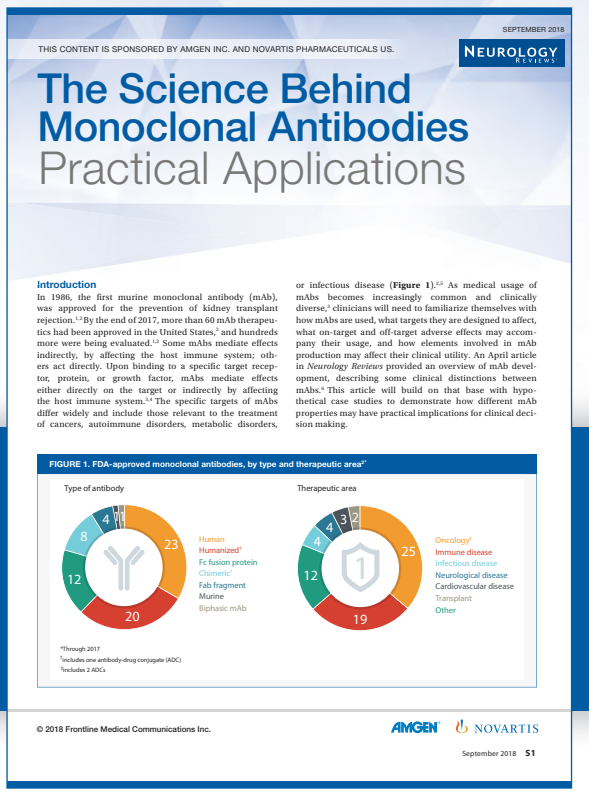
Cholesterol Treatment Trialists' Collaboration. Efficacy and saftery of statin therapy in older people: a meta-analysis of individual participant data from 28 randomized controlled trials. *Lancet*. 2019;393(10170):407-415.

This content is sponsored by Amgen Inc. and Novartis Pharmaceuticals Corporation.

The Science Behind Monoclonal Antibodies
Practical Applications

Review hypothetical case studies that explore different monoclonal antibody (mAb) properties and the practical applications for clinical decision making.



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NEUROLOGY REVIEWS

The Science Behind Monoclonal Antibodies
Practical Applications

Introduction

In 1986, the first murine monoclonal antibody (mAb), was approved for the prevention of kidney transplant rejection.[1,2] By the end of 2017, more than 60 mAb therapeutics had been approved in the United States,[3] and hundreds more were being evaluated.[1,2] Some mAbs mediate effects indirectly, by affecting the host immune system; others act directly. Upon binding to a specific target receptor, protein, or growth factor, mAbs mediate effects either directly on the target or indirectly by affecting the host immune system.[1,3] The specific targets of mAbs differ widely and include those relevant to the treatment of cancers, autoimmune disorders, metabolic disorders, or infectious disease (**Figure 1**).[2,3] As medical usage of mAbs becomes increasingly common and clinically diverse,[3] clinicians will need to familiarize themselves with how mAbs are used, what targets they are designed to affect, what on-target and off-target adverse effects may accompany their usage, and how elements involved in mAb production may affect their clinical utility. An April article in *Neurology Reviews* provided an overview of mAb development, describing some clinical distinctions between mAbs.[4] This article will build on that base with hypothetical case studies to demonstrate how different mAb properties may have practical implications for clinical decision making.

FIGURE 1. FDA-approved monoclonal antibodies, by type and therapeutic area*

Type of antibody

Therapeutic area

*Through 2017
†Includes one antibody-drug conjugate (ADC)
‡Includes 2 ADCs

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This content can be found in the September issue of Neurology Reviews, in the Education Center at the *Neurology Reviews* website, and directly at **www.mdedge.com/neurologyreviews/PracticalApplicationsofMAbs**

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Many hospitals are meeting treatment goals set by the Target: Stroke program

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in thrombolytic speed played out in improved patient outcomes. During phase 2 of Target: Stroke, which ran from January 2014 to September 2018, 85,078 U.S. patients received tPA at one of the participating hospitals. During those 4 years, the rate of in-hospital mortality was 6.0%, half the patients were discharged home, 53% could walk independently, and the rate of intracerebral hemorrhage (ICH) was 3.5%. The researchers compared these clinical event rates with the rates from 24,603 tPA-treated patients during 2003–2009, before the Target: Stroke campaign began. After adjustment for many potential confounders, the more recently treated cohort had a 31% relative risk reduction in in-hospital mortality, a 43% relative increase in being discharged home, a 40% relative increase in independent ambulation, and a 32% relative risk reduction in the rate of symptomatic ICH. All these between-group differences were statistically significant.

> **Recent years have seen a 31% relative risk reduction in in-hospital mortality and a 32% relative risk reduction in the rate of symptomatic ICH.**

"We were hoping that by improving DTN times we could achieve improved outcomes, but often in quality-improvement research—even when the process of care improves—the gains in outcomes don't necessarily match expectations. Fortunately, with Target: Stroke, the remarkable improvements in timely treatment translated to remarkable improvements in clinical outcomes," Dr. Fonarow said in an interview. "These are substantial, clinically relevant improvements in clinical outcomes for patients with acute ischemic stroke. As a result of the program, more than 100,000 acute ischemic stroke patients received much more timely acute ischemic stroke care and achieved far better clinical outcomes."

During the 2003–2018 period, the percentage of presenting acute ischemic stroke patients who received tPA treatment at the 913 Get With The Guidelines hospitals that participated in the Target: Stroke program (and thus had reviewable data) throughout all three periods rose from 6% during 2003–2009 (prestudy) to 8% during 2010–2013 (phase 1) and to 12% during 2014–2018 (phase 2). The percentages of these patients who received the drug within 60 minutes were 27% during 2003–2009, 43% during 2010–2013, and 68% during the entire 2014–2018 period, culminating in the 75% rate during July–September 2018, reported Dr. Fonarow, professor of medicine and cochief of cardiology at the University of California, Los Angeles.

Dr. Fonarow attributed the drop in the rate of ICH—from 5.7% during 2003–2009 to 4.4% during 2010–2013 and down to 3.5% during 2014–2018—to the faster delivery of tPA. "With faster treatment, there is less ischemic brain and vascular damage and thus a lower likelihood of ICH as a complication of tPA," he explained.

Programs promoted best practices

The Target: Stroke program achieved these gains in speedier thrombolytic treatment (and better recognition of eligible patients) through educational and promotional activities, including dissemination of best practices. Notable best practices have included EMS prenotification of hospitals before they arrive with a stroke patient, direct transport of patients to a brain imaging scanner, premix of tPA, initiation of tPA in the brain imaging suite, and prompt data feedback, Dr. Fonarow said.

The Get With the Guidelines-Stroke and Target: Stroke programs now involve more than 2,100 U.S. hospitals, and they are able to deliver emergency care to roughly 70% of U.S. acute ischemic stroke patients, he noted.

With achievement of Target: Stroke's phase 2 goals, the program announced its launch of a third phase, with new treatment goals: initiation of thrombolytic treatment to 85% of eligible patients within 60 minutes, to 75% within 45 minutes, and to 50% within 30 minutes. The phase 3 Target: Stroke program also for the first time includes treatment goals for delivery of endovascular thrombectomy treatment. **NR**

—Mitchel L. Zoler

Thrombolytic goal achievement documents real progress

The Target: Stroke and Get With the Guidelines-Stroke programs should be commended for the impressive achievements they have made in improved delivery of thrombolytic therapy to acute ischemic stroke patients. What's happened over the past decade in the speed of delivery of tissue plasminogen activator for treating U.S. stroke patients has been a real success story.

Tissue plasminogen activator received U.S. approval for acute stroke treatment in 1996, but during the first 10 years or so, it hardly moved. It took programs like Target: Stroke to make rapid thrombolysis a true part of routine care. Over the past 10 years, more clinicians have become comfortable with a systematic approach to care delivery; it has been a great transformation. The successes with thrombolytic therapy give us a model to apply to other aspects of acute stroke care that could also benefit from a systematic approach. Endovascular thrombectomy, for example, has been able to piggyback on the assessment, triage, and delivery systems that were first developed to deal with thrombolytic therapy.

Programs like Get With the Guidelines and Target: Stroke have proven their value, but a significant barrier remains to bringing this program to all U.S. stroke patients and to all U.S. hospitals that treat stroke patients. That barrier is resources. Participating hospitals need to meet certain data-collection standards, but some U.S. hospitals do not have the resources to do this.

Bruce Ovbiagele, MD, is a neurologist and chief of staff for the San Francisco Veterans Affairs Health Care System. He had no disclosures. He made these comments in an interview.

High prevalence of sleep problems in children with autism spectrum disorder

Children with ASD are more likely to have anxiety, which may predispose them to sleep problems.

Children with a diagnosis of autism spectrum disorder (ASD) or another developmental delay or disorder that includes autistic characteristics are twice as likely to have sleeping problems, a multisite case–control study has found.

The findings match up with those of previous similar studies, but this study is among the largest to measure sleeping problems in children with ASD with two control groups.

"The higher reported occurrence of sleep problems in children with ASD may be due to multiple contributing factors, including physiologic differences, sleep disorders, developmental comorbidities, medical comorbidities causing sleep disruption, communication impairments, and behavioral disturbances," Ann M. Reynolds, MD, of the University of Colorado and Children's Hospital Colorado, both in Aurora, and her associates reported in *Pediatrics*.

"Children with ASD are more likely to have anxiety, which may predispose them to sleep problems," the authors added.

Comparing 3 groups of children

The study evaluated sleep habits and problems in 1,987 children aged 2–5 years. The study population included 522 children with ASD, 228 children with other developmental delays and disorders that have ASD characteristics, 534 children with other developmental delays and disorders, and 703 children from the general population.

Parents completed the Children Sleep Habits Questionnaire (CSHQ), a 33-item assessment tool typically used with a total score cutoff of 41 or above for identification of children with sleep disorders. The researchers also used a second, more conservative cutoff of 48—the cutoff for the highest quartile in the general population group—to avoid overidentification with the lower cutoff.

Scores were adjusted for maternal education and race/ethnicity, family income, child age and sex, and child cognitive scores on the Mullen Scales of Early Learning (MSEL). The researchers also adjusted for genetic and neurologic diagnoses, including Down syndrome, fragile X syndrome, Rett syndrome, tuberous sclerosis, cerebral palsy, and neurofibromatosis.

ASD was associated with impaired cognition

Autistic children tended to have lower MSEL scores than the other children. The autistic children and those with other developmental disorders and delays were more likely than those in the general population to have neurologic or genetic conditions.

Based on a cutoff score of 48, autistic children had more than double the odds of sleep problems, compared with children in the general population (adjusted odds ratio [aOR], 2.37) and children with other developmental delays (aOR, 2.12).

Using a cuttoff of 41 among children with ASD, the odds of sleep problems were 1.45 times greater than the general population and 1.75 times greater than those with developmental delays.

But children with developmental delays who displayed autistic characteristics did not have a significantly different prevalence of sleep problems than children with ASD had.

"The phenotypic overlay between children with ASD and children with developmental delay with ASD [characteristics] may explain the similarities in sleep disturbance among these two groups," the authors wrote. Both groups have "higher rates of obsessive–compulsive symptoms, self-injurious behavior, ADHD symptoms, and developmental and communication impairments" than children with developmental delays without autistic characteristics.

The research was funded by the Centers for Disease Control and Prevention, the National Institutes of Health, and the National Center for Advancing Translational Sciences Colorado Clinical and Translational Science Award. Dr. Reynolds consults for Ovid Therapeutics regarding evaluation of sleep severity and improvement in clinical trials. No other authors had disclosures.

Cooperation is key to addressing ASD sleep problems

It is possible to reduce night waking and improve sleep onset within 5-15 weeks after parents have been trained. "Successful behavioral programs include bedtime fading, teaching healthy sleep practices, and increasing a child's physical activity during the day," said Catherine Lord, PhD, professor of psychiatry and biobehavioral sciences at the University of California, Los Angeles, in an accompanying editorial. Although research supports melatonin as an effective intervention for helping children fall asleep and sleep longer, the high percentage of children in the study already taking melatonin reveals its limitations. "Thus, it is recommended that families try behavioral programs before trials with melatonin," she said.

Families and providers can only work together to address sleep issues if providers ask about sleep concerns, help families implement interventions, and follow up with progress. "In most cases, this help does not have to come from sleep experts, but does require dedicated time and effort using the now-growing base of evidence about effective interventions," she concluded.

Dr. Lord reports royalties from diagnostic instruments used in this study that were donated to a not-for-profit agency. She is supported by grants from the National Institutes of Health and Simons Foundation Autism Research Initiative. **NR**

—Tara Haelle

Suggested Reading

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DBS provides motor and nonmotor benefits for as long as 2 years after implantation

continued from page 1

Vercise DBS systems at 70 international sites. These systems enable multiple independent current source control.

Participants presented for clinical visits at 3 months, 6 months, 1 year, 2 years, and 3 years after surgery. Jan Vesper, MD, PhD, professor of neurosurgery at Heinrich Heine University in Düsseldorf, Germany, and his colleagues analyzed patient outcomes, including the Parkinson's Disease Questionnaire (PDQ-39), Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Clinical Global Impression of Change (as assessed by the patient, caregiver, and clinician), and the Schwab and England (SE) scale. The researchers also reported adverse events.

As of November 2018, 403 participants had been enrolled in the registry, and 359 had undergone DBS implantation. At baseline, mean age was 59.6 years, and approximately 70% of participants were male. Mean disease duration was 10.4 years. Without medication, mean MDS-UPDRS III score was 44.8, and mean PDQ-39 Summary Index score was 28.8.

> Participants had a sustained benefit on quality of life, as assessed by the PDQ-39 Summary Index Score.

At 1 year, participants' mean off-medication MDS-UPDRS III score was 29.7. This result represented a significant 34% improvement in motor performance.

PDQ-39 Summary Index score was improved by 6.7 points at 6 months, 4.7 points at 1 year, and 3.0 points at 2 years, which represented a sustained benefit for participants' quality of life. Improvements in activities of daily living were sustained throughout the 2-year period. Cognition was improved at 6 months, but not at subsequent visits. Mobility, stigma, and bodily discomfort were improved at 6 months and 1 year, but not at 2 years. Furthermore, more than 80% of patients, caregivers, and clinicians observed improvements in Parkinson's disease symptoms at all time points.

The investigators did not find any unanticipated adverse events. In all, 217 serious adverse events occurred in 121 participants. Of these events, 60 were related to stimulation. No lead fractures or breakages occurred.

Jan Vesper, MD, PhD

"This registry represents the first large-scale collection of outcomes using a DBS system capable of multiple independent current source control," said Dr. Vesper and colleagues.

The investigators did not report any conflicts of interest. **NR**

—Erik Greb

Functional MRI detects consciousness after brain damage

Four brain signal coordination patterns emerge with differences across levels of consciousness.

Functional MRI can measure patterns of connectivity to determine levels of consciousness in nonresponsive patients with brain injury, according to results from a multicenter, cross-sectional, observational study.

Blood oxygen level–dependent (BOLD) fMRI showed that brain-wide coordination patterns of high complexity became increasingly common moving from unresponsive patients to those with minimal consciousness to healthy individuals, reported lead author Athena Demertzi, PhD, of GIGA Research Institute at the University of Liège in Belgium, and her colleagues.

In search of markers of consciousness

"Finding reliable markers indicating the presence or absence of consciousness represents an outstanding open problem for science," the investigators wrote in *Science Advances*.

In medicine, an fMRI-based measure of consciousness could supplement behavioral assessments of awareness and guide therapeutic strategies. More broadly, image-based markers could help elucidate the nature of consciousness itself.

"We postulate that consciousness has specific characteristics that are based on the temporal dynamics of ongoing brain activity and its coordination over distant cortical regions," the investigators wrote. "Our hypothesis stems from the common stance of various contemporary theories which propose that consciousness relates to a dynamic process of self-sustained, coordinated brain-scale activity assisting the tuning to a constantly evolving environment, rather than in static descriptions of brain function."

There is a need for a reliable way of distinguishing consciousness from unconscious states, the investigators said. "Given that nonresponsiveness can be associated with a variety of brain lesions, varying levels of vigilance, and covert cognition, we highlight the need to determine a common set of features capable of accounting for the capacity to sustain conscious experience."

Patients were imaged under anesthesia or at rest

To search for patterns of brain signal coordination that correlate with consciousness, four independent research centers performed BOLD fMRI scans of participants at rest or under anesthesia with propofol. Of 159 total participants, 47 were healthy individuals and 112 were patients in a vegetative state with unresponsive wakefulness syndrome (UWS) or in a minimally conscious state (MCS), based on standardized behavioral assessments. The main data analysis, which included 125 participants, assessed BOLD fMRI signal coordination between six brain networks known to have roles in cognitive and functional processes.

The researchers' analysis revealed four distinct and recurring brain-wide coordination patterns ranging on a scale from highest activity (pattern 1) to lowest activity (pattern 4). Pattern 1, which exhibited most long-distance edges, spatial complexity, efficiency, and community structure, became increasingly common when moving from UWS patients to MCS patients to healthy control individuals.

In contrast, pattern 4, characterized by low interareal coordination, showed an inverse trend; it became less common when moving from vegetative patients to healthy individuals. Although patterns 2 and 3 occurred with equal frequency across all groups, the investigators noted that switching between patterns was most common and predictably sequential in healthy individuals, versus patients with UWS, who were least likely to switch patterns. A total of 23 patients who were scanned under propofol anesthesia were equally likely to exhibit pattern 4, regardless of health status, suggesting that pattern 4 depends upon fixed anatomical pathways. Results were not affected by scanning site or other patient characteristics, such as age, gender, etiology, or chronicity.

Brain signal coordination indicates brain state

"We conclude that these patterns of transient brain signal coordination are characteristic of conscious and unconscious brain states," the investigators wrote, "warranting future research concerning their relationship to ongoing conscious content and the possibility of modifying their prevalence by external perturbations, both in healthy and pathological individuals, as well as across species."

The study was funded by a James S. McDonnell Foundation Collaborative Activity Award, INSERM, the Belgian National Funds for Scientific Research, the Canada Excellence Research Chairs program, and others. The authors declared having no conflicts of interest.

NR

—Will Pass

Suggested Reading

Demertzi A, Tagliazucchi E, Dehaene S, et al. Human consciousness is supported by dynamic complex patterns of brain signal coordination. *Sci Adv.* 2019;5(2):eaat7603.

Acute flaccid myelitis has unique MRI features

Acute flaccid myelitis more commonly presents with asymmetric paralysis and spinal cord lesions largely restricted to gray matter.

Acute flaccid myelitis appears to present most commonly as asymmetric weakness after respiratory viral infection and has distinctive MRI features that could help with early diagnosis. In a paper published online ahead of print November 30, 2018, in JAMA Pediatrics, researchers presented the results of a retrospective case series of 45 children who were diagnosed between 2012 and 2016 with acute flaccid myelitis, or "pseudo polio," using the Centers for Disease Control's case definition.

Matthew J. Elrick, MD, PhD, of Johns Hopkins University, Baltimore, and his coauthors came up with a set of reproducible and distinctive features of acute flaccid myelitis. These were the presence of a prodromal fever or viral syndrome; weakness in a lower motor neuron pattern involving one or more limbs, neck, face, and/or bulbar muscles; supportive evidence either from MRI, nerve conduction studies, or cerebrospinal fluid; and the absence of objective sensory deficits, supratentorial white matter, cortical lesions greater than 1 cm in size, encephalopathy, elevated cerebrospinal fluid without pleocytosis, or any other alternative diagnosis.

The researchers commented that, while the CDC case definition has helped with epidemiologic surveillance of acute flaccid myelitis, it may also pick up children with acute weakness caused by other conditions such as transverse myelitis, Guillain-Barré syndrome, ischemic myelopathy, and other myelopathies.

Is the CDC case definition adequate?

To identify clinical features that might help differentiate patients with acute flaccid myelitis, the researchers attempted to see how many alternative diagnoses were captured in the CDC case definition.

The patients in their study all presented with acute flaccid paralysis in at least one limb and with either an MRI showing a spinal cord lesion spanning one or more spinal segments but largely restricted to gray matter or pleocytosis of the cerebrospinal fluid. The researchers divided the cases into those who also met a well-defined alternative diagnosis—whom they categorized as "acute flaccid myelitis with possible alternative diagnosis" (AFM-ad)—and those who were categorized as "restrictively defined accute flaccid myelitis" (rAFM). Overall, 34 patients were classified as rAFM and 11 as AFM-ad.

Those in the rAFD group nearly all had asymmetric onset of symptoms, while those in the AFM-ad group were more likely to experience bilateral onset in their lower extremities, "reflecting the pattern of symptoms often seen in other causes of myelopathy such as transverse myelitis and ischemic injury," the authors said.

While both groups often presented with decreased muscle tone and reflexes, this was more likely to evolve to increased tone or hyperreflexia in the AFM-ad group. Patients with AFM-ad were also more likely to experience impaired bowel or bladder function.

On MRI, lesions were mostly or completely restricted to the spinal cord gray matter in patients with rAFM or to involve the dorsal pons. These patients did not have any supratentorial brain lesions.

Patients in the rAFM category also had lower cerebrospinal fluid protein values than those in the AFM-ad category, but this was the only cerebrospinal fluid difference between the two groups.

All patients categorized as having rAFM had an infectious prodrome—such as viral syndrome, fever, congestion, and cough—compared with 63.6% of the patients categorized as AFM-ad. The pathogen was identified in only 13 of the rAFM patients, and included 5 patients with enterovirus D68, 2 with unspecified enterovirus, 2 with rhinovirus, 2 with adenovirus, and 2 with mycoplasma. Of the 3 patients in the AFM-ad group whose pathogen was identified, 1 had an untyped rhinovirus/enterovirus and mycoplasma, 1 had a rhinovirus B, and 1 had enterovirus D68.

"These results highlight that the CDC case definition, while appropriately sensitive for epidemiologic ascertainment of possible acute flaccid myelitis cases, also encompasses other neurologic diseases that can cause acute weakness," the authors wrote. However, they acknowledged that acute flaccid myelitis was still poorly understood and their own definition of the disease may change as more children are diagnosed.

"We propose that the definition of rAFM presented here be used as a starting point for developing inclusion and exclusion criteria for future research studies of acute flaccid myelitis," they wrote.

> Confirming the diagnosis requires lumbar puncture and MRI of the spinal cord.

The study was supported by Johns Hopkins University, the Bart McLean Fund for Neuroimmunology Research, and Project Restore. Two authors reported funding from private industry outside the submitted work and five reported support from or involvement with research and funding bodies.

High index of suspicion required

Acute flaccid myelitis initially presents subtly, complicating its diagnosis, said Sarah E. Hopkins, MD; Matthew J. Elrick, MD, PhD; and Kevin Messacar, MD, in an accompanying editorial. Dr. Hopkins is from the division of neurology at the Children's Hospital of Philadelphia, Dr. Elrick is from the department of neurology at Johns Hopkins University, Baltimore, and Dr. Messacar is from the department of pediatrics at the Children's Hospital Colorado.

Children present with a rapid onset of weakness that is associated with a febrile illness, which can be respiratory, gastrointestinal, or with symptoms of hand-foot-and-mouth disease. Given the lack of effective treatments, early diagnosis and monitoring are essential for mitigating the risk of respiratory decline and long-term complications.

While patient history and physical examination can provide clues to the presence of acute flaccid myelitis, confirming the diagnosis requires lumbar puncture and MRI of the spinal cord, they said. On MRI, diagnostic confirmation will come from findings of longitudinal, butterfly-shaped, anterior horn–predominant T2 and fluid-attenuated inversion recovery hyperintensities of the central gray matter.

Patients with suspected acute flaccid myelitis should be hospitalized because they can rapidly deteriorate to the point of respiratory compromise, particularly those with upper extremity and bulbar weakness. **NR**

—Bianca Nogrady

Suggested Reading

Elrick MJ, Gordon-Lipkin E, Crawford TO, et al. Clinical subpopulations in a sample of North American children diagnosed with acute flaccid myelitis, 2012-2016. *JAMA Pediatr.* 2018 Nov 30 [Epub ahead of print].

Hopkins SE, Elrick MJ, Messacar K. Acute flaccid myelitis—keys to diagnosis, questions about treatment, and future directions. *JAMA Pediatr.* 2018 Nov 30 [Epub ahead of print].

Compounded pain creams no better than placebo creams in localized chronic pain

At 1 month, creams specifically formulated for neuropathic, nociceptive, or mixed pain had no effect beyond placebo.

Specially formulated topical pain creams are no better than placebo creams for relieving localized chronic pain, according to results from a double-blind, randomized, placebo-controlled trial.

Study authors led by Robert E. Brutcher, PharmD, PhD, of Walter Reed National Military Medical Center in Bethesda, Md., said their findings, published online ahead of print Feb. 4 in the *Annals of Internal Medicine*, suggest compounded pain creams should not be routinely used for chronic pain conditions.

The researchers noted that the use of compounded topical pain creams has increased dramatically despite "weak evidence" supporting their efficacy to treat localized pain, and this is particularly the case in military personnel, where the authors said treatments without central effect may be particularly beneficial because "opioid therapy may render a service member nondeployable and medications that affect the central nervous system may have a negative effect on judgment and motor skills."

They noted a report from the U.S. Government Accountability Office that showed Tricare's pharmacy benefits program paid $259 million for compounded medications in the 2013 fiscal year, a figure that increased to $746 million in 2014.

"The soaring costs, coupled with sparse efficacy data prompted the Defense Health Agency to evaluate this issue," they wrote.

The objectives of the current study were to assess the efficacy of compounded pain creams for chronic pain conditions and determine whether efficacy differed for the various pain classifications. "We hypothesized that, compared with placebo, compounded topical pain creams would provide greater pain relief and functional improvement," they said.

Putting pain creams to the test

The randomized trial involved 133 patients diagnosed with neuropathic pain, 133 with nociceptive pain, and 133 with mixed pain who had attended pain clinics at Walter Reed. Patients were between ages 18 and 90 and had localized pain in the face, back or buttocks, neck, abdomen, chest, groin, or in up to two extremities. To be included in the study, patients also were required to have an average pain score of 4 or greater on a 10-point numerical rating scale during the preceding week and have symptoms lasting longer than 6 weeks.

Patients in all three pain subgroups were randomized in a 1:1 ratio to receive either a compounded pain cream or a placebo cream. The authors noted that their "pain cream formulations were selected on the basis of accepted systemic indications for neuropathic and nociceptive pain."

The formulation given to participants with neuropathic pain (n = 68) contained 10% ketamine, 6% gabapentin, 0.2% clonidine, and 2% lidocaine. The patients with nociceptive pain (n = 66) received a cream with 10% ketoprofen, 2% baclofen, 2% cyclobenzaprine, and 2% lidocaine. Those with mixed pain (n = 68) were given a cream containing 10% ketamine, 6% gabapentin, 3% diclofenac, 2% baclofen, 2% cyclobenzaprine, and 2% lidocaine. The authors said the concentrations of individual medications were based on previous trials that evaluated topical use.

The patients, who had a mean age across the groups that ranged from 48 to 57 years, applied cream to affected areas three times per day, with the amount dispensed determined by the size of the area experiencing pain. About half of the patients were women.

The primary outcome measures were an average pain score 1 month after treatment. A positive categorical response was a reduction in pain score of 2 or more points, coupled with a score above 3 on a 5-point satisfaction scale. Secondary outcomes included Short Form-36 Health Survey scores, satisfaction, and categorical response. Participants with a positive outcome were followed to 3 months.

Change in the primary outcome of average pain score at 1 month did not differ between the active cream and placebo groups for any type of pain classification. The change was –0.1 points (95% confidence interval, –0.8 to 0.5 points) for neuropathic pain, –0.3 points (95% CI, –0.9 to 0.2 points) for nociceptive pain, and –0.3 points (95% CI, –0.9 to 0.2 points) for mixed pain.

Among all patients combined, an overall change in average pain scores of –0.3 points (95% CI, –0.6 to 0.1 points) that favored the active-ingredient cream also did not differ between the treatment and placebo groups.

"The lower 95% confidence bounds for the 1-month between-group differences were all 0.9 points or less and excluded clinically meaningful benefits with the compounded topical pain cream," the authors wrote.

Secondary outcomes also did not differ between the two study groups for any type of pain classification or for the entire cohort.

"Although participants in both treatment and control groups had improvement in their pain throughout the study, no significant differences were observed in pain scores, functional improvement, or satisfaction in the cohort or in any subgroup," the authors concluded.

They noted that their findings were consistent with previous studies that also showed a lack of efficacy for most topical pain creams.

Not recommended for routine use

While some randomized trials have suggested positive findings for capsaicin, lidocaine, and NSAIDs, the authors noted that they did not find a similar benefit in their study population. "Administered as stand-alone agents, lidocaine and NSAIDs may alleviate pain, although the effect size is small and the number needed to treat is large," they wrote.

"Considering the increased costs of using a non–FDA-approved and regulated compounded cream rather than a single agent, we caution against routine use of compounded creams for chronic pain," they wrote.

They noted that their study had several limitations, including that conventional treatments had failed in some of the participants before they enrolled in the study, increasing the likelihood that subsequent therapy would not be effective.

The authors suggested that future studies should aim to establish whether targeting specific types of pain or adding other agents like dimethyl sulfoxide would result in better outcomes.

The Centers for Rehabilitation Sciences Research in the U.S. Department of Defense's Defense Health Agency funded the study. Two authors reported receiving grants and personal fees from several pharmaceutical companies. **NR**

—Nicola Garrett

Suggested Reading

Brutcher RE, Kurihara C, Bicket MC, et al. Compounded topical pain creams to treat localized chronic pain: a randomized controlled trial. *Ann Intern Med.* 2019 Feb 5 [Epub ahead of print].