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Population-level rate of SUDEP may have decreased

NEW ORLEANS—The population-level rate of sudden unexpected death in epilepsy (SUDEP) may have decreased over time, according to data described at the annual meeting of the American Epilepsy Society. Whether this decrease resulted from an improved understanding of SUDEP risk or a focus on risk-reduction strategies is unknown, said Daniel Friedman, MD, associate professor of neurology at New York University Langone Health.

In addition, the rates of SUDEP in various populations differ according to their socioeconomic status. Differences in access to care are a potential, but unconfirmed, explanation for this association, said Dr. Friedman. Another possible explanation is that confounders such as mental health disorders, substance abuse, and insufficient social support affect individuals' ability to manage their disorder.

Dr. Friedman and colleagues initially examined SUDEP rates over time in a cohort of patients who received vagus nerve stimulator (VNS) implantation for drug-resistant epilepsy. They analyzed data for 40,443 patients who underwent surgery during 1988–2012. The age-adjusted SUDEP rate per 1,000 person-years of follow-up decreased significantly from 2.47 in years 1–2 to 1.68 in years 3–10. "There was no control group, so we couldn't necessarily

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Frailty may affect the expression of dementia

Among people of the same age, the degree of frailty influences the association between Alzheimer's disease pathology and Alzheimer's dementia, according to research published in the February issue of *Lancet Neurology*. Data suggest that frailty reduces the threshold for Alzheimer's disease pathology to cause cognitive decline. Frailty also may contribute to other mechanisms that cause dementia, such as inflammation and immunosenescence, said the investigators.

"While more research is needed, given that frailty is potentially reversible, it is possible that helping people to maintain function and independence in later life could reduce both dementia risk and the severity of debilitating symptoms common in this disease," said Professor Kenneth Rockwood, MD, of the Nova Scotia Health Authority and Dalhousie University in Halifax, Nova Scotia.

More susceptible to dementia?

The presence of amyloid plaques and neurofibrillary tangles is not a sufficient condition for the clinical expression of dementia. Some patients with a high degree of Alzheimer's disease pathology have no apparent cog-

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Frailty reduces the threshold for Alzheimer's disease pathology to cause cognitive decline

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nitive decline. Other factors therefore may modify the relationship between pathology and dementia.

Most people who develop Alzheimer's disease dementia are older than 65 years, and many of these patients are frail. Frailty is understood as a decreased physiologic reserve and an increased risk for adverse health outcomes. Dr. Rockwood and his colleagues hypothesized that frailty moderates the clinical expression of dementia in relation to Alzheimer's disease pathology.

To test their hypothesis, the investigators performed a cross-sectional analysis of data from the Rush Memory and Aging Project, which collects clinical and pathologic data from adults older than 59 years without dementia at baseline who live in Illinois. Since 1997, participants have undergone annual clinical and neuropsychological evaluations, and the cohort has been followed for 21 years. For their analysis, Dr. Rockwood and his colleagues included participants without dementia or with Alzheimer's dementia at their last clinical assessment. Eligible participants had died, and complete autopsy data were available for them.

The researchers measured Alzheimer's disease pathology using a summary measure of neurofibrillary tangles and neuritic and diffuse plaques. Clinical diagnoses of Alzheimer's dementia were based on clinician consensus. Dr. Rockwood and his colleagues retrospectively created a 41-item frailty index from variables (e.g., symptoms, signs, comorbidities, and function) that were obtained at each clinical evaluation.

Logistic regression and moderation modeling allowed the investigators to evaluate relationships between Alzheimer's disease pathology, frailty, and Alzheimer's dementia. Dr. Rockwood and his colleagues adjusted all analyses for age, sex, and education.

In all, 456 participants were included in the analysis. The sample's mean age at death was 89.7 years, and 69% of participants were women. At participants' last clinical assessment, 242 (53%) had possible or probable Alzheimer's dementia.

The sample's mean frailty index was 0.42. The median frailty index was 0.41, a value similar to the threshold commonly used to distinguish between moderate and severe frailty. People with high frailty index scores (i.e., 0.41 or greater) were older, had lower Mini-Mental State Examination scores, were more likely to have a diagnosis of dementia, and had a higher Braak stage than those with moderate or low frailty index scores.

Significant interaction between frailty and Alzheimer's disease

After the investigators adjusted for age, sex, and education, frailty (odds ratio, 1.76) and Alzheimer's disease pathology (OR, 4.81) were independently associated with Alzheimer's dementia. When the investigators added frailty to the model for the relationship between Alzheimer's disease pathology and Alzheimer's dementia, the model fit improved. They found a significant interaction between frailty and Alzheimer's disease pathology (OR, 0.73). People with a low amount of frailty were better able to tolerate Alzheimer's disease pathology, and people with higher amounts of frailty were more likely to have more Alzheimer's disease pathology and clinical dementia.

One of the study's limitations is that it is a secondary analysis, according to Dr. Rockwood and his colleagues. In addition, frailty was measured close to participants' time of death, and the measurements may thus reflect terminal decline. Participant deaths resulting from causes other than those related to dementia might have confounded the results. Finally, the sample came entirely from people living in retirement homes in Illinois, which might have introduced bias. Future research should use a population-based sample, said the authors.

Frailty could be a basis for risk stratification and could inform the management and treatment of older adults, said Dr. Rockwood and his colleagues. The study results have "the potential to improve our understanding of disease expression, explain failures in pharmacologic treatment, and aid in the development of more appropriate therapeutic targets, approaches, and measurements of success," they concluded.

Results suggest strategies for delaying dementia onset

The results of the study by Rockwood and colleagues confirm the strong links between frailty and Alzheimer's disease and other dementias, said Francesco Panza, MD, PhD, of the University of Bari (Italy) Aldo Moro, and his colleagues in an accompanying editorial.

Frailty is primary or preclinical when it is not directly associated with a specific disease or when the patient has no substantial disability. Frailty is considered secondary or clinical when it is associated with known comorbidities (e.g., cardiovascular disease or depression). "This distinction is central in identifying frailty phenotypes with the potential to predict and prevent dementia, using novel models of risk that introduce modifiable factors," wrote Dr. Panza and his colleagues.

"In light of current knowledge on the cognitive frailty phenotype, secondary preventive strategies for cognitive impairment and physical frailty can be suggested," they added. "For instance, individualized multidomain interventions can target physical, nutritional, cognitive, and psychological domains that might delay the progression to overt dementia and secondary occurrence of adverse health-related outcomes, such as disability, hospitalization, and mortality."

The study had no source of funding. The study authors reported receiving fees and grants from DGI Clinical, GlaxoSmithKline, Pfizer, and Sanofi. Authors also received support from governmental bodies such as the National Institutes of Health and the Canadian Institutes of Health Research. The editorialists declared no competing interests. **NR**

—Erik Greb

Suggested Reading

Panza F, Lozupone M, Logroscino G. Understanding frailty to predict and prevent dementia. *Lancet Neurol.* 2019;18(2):133-134.

Wallace LMK, Theou O, Godin J, et al. Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project. *Lancet Neurol.* 2019;18(2):177-184.

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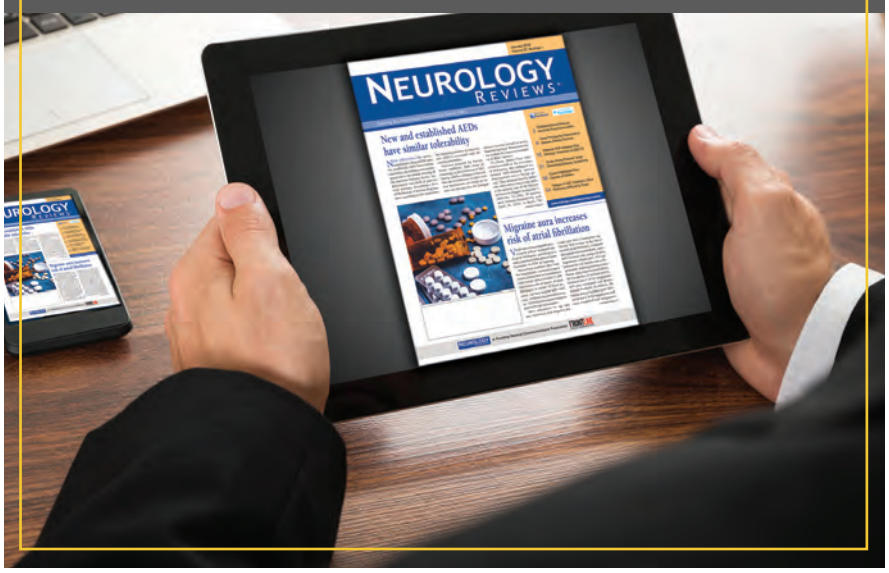

Data indicate a decline over time in the incidence of SUDEP

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attribute the SUDEP rate reduction to the intervention," said Dr. Friedman. A study by Tomson et al. of patients with epilepsy who received VNS implantation had similar findings.

The literature about the mechanisms of SUDEP and reduction of SUDEP risk has increased in recent years. Neurologists have advocated for greater disclosure to patients of SUDEP risk, as well as better risk counseling. Dr. Friedman and his colleagues decided to investigate whether these factors have affected the risk of SUDEP during the past decade.

They retrospectively examined data for people whose deaths had been investigated at medical examiner's offices in New York City, San Diego County, and Maryland. They focused on decedents for whom epilepsy or seizure was listed as a cause or contributor to death or as a comorbid condition on the death certificate. They reviewed all available reports, including investigator notes, autopsy reports, and medical records. Next, Dr. Friedman and his colleagues calculated the annual SUDEP rate as a proportion of the general population, estimated using annual Census and American Community Survey data.

The estimated rate of SUDEP decreased by about 36% from 2009–2010 to 2014–2015. SUDEP rates as a proportion of the total population also declined.

They used the Mann-Kendall test to analyze the trends in SUDEP rate during 2009–2015.

Of 1,466 deaths in people with epilepsy during this period, 1,124 were classified as definite SUDEP, probable SUDEP, or near SUDEP. Approximately 63% of SUDEP cases were male, and 45% were African American. The mean age at death was 38 years.

Dr. Friedman's group found a significant decrease in the overall incidence of SUDEP in the total population during 2009–2015. When they examined the three regions separately, they found decreases in SUDEP incidence in New York City and Maryland, but not in San Diego County. They found no difference in SUDEP rates by season or by day of the week.

In a subsequent analysis, Dr. Friedman and his colleagues adjudicated all deaths related to seizure and epilepsy in the three regions during 2009–2010 and 2014–2015 and identified all cases of definite and probable SUDEP. The estimated rate of SUDEP decreased by about 36% from the first period to the second period. SUDEP rates as a proportion of the total population in those regions also declined.

The investigators also examined differences in estimated SUDEP rates in the United States according to median household income. In New York, the zip codes with the highest SUDEP rates tended to have the lowest median household incomes. The zip codes in the lowest quartile of family household income had a SUDEP rate more than twice as high as that in the zip codes in the highest income quartile. This association held true for the period from 2009–2010 and for 2014–2015.

Dr. Friedman and colleagues received funding from Finding a Cure for Epilepsy and Seizures, which is affiliated with the NYU Comprehensive Epilepsy Center and NYU Langone Health.

NR

—Erik Greb

AAN publishes position statement on brain death

The association calls for uniform laws and policies regarding brain death, as well as continued research and public education.

In a position statement published online ahead of print Jan. 2 in *Neurology*, the American Academy of Neurology (AAN) urges uniformity in the laws, policies, and practices related to brain death. Such uniformity would reduce uncertainty and improve patient care, according to the authors. The statement, which was drafted by the AAN's Brain Death Working Group, also supports the development of uniform policies regarding brain death and its determination within American medical institutions. Finally, the document provides neurologists with guidance for responding to requests for accommodation, including objections to the determination of brain death and to the withdrawal of organ-sustaining technology.

The AAN defines brain death as death resulting from irreversible loss of function of the entire brain. The Uniform Determination of Death Act of 1981 held that brain death and circulatory death (that is, death resulting from irreversible loss of function of the circulatory system) are equivalent, and the AAN acknowledges this equivalence.

The two current medical standards for brain death are the AAN's 2010 Evidence-Based Guideline Update: Determining Brain Death in Adults and the 2011 Guidelines for the Determination of Brain Death in Infants and Children, which was published by the pediatric section of the Society of Critical Care Medicine, the sections of neurology and critical care of the American Academy of Pediatrics, and the Child Neurology Society. "The AAN is unaware of any cases in which compliant application of the brain death guidelines led to inaccurate determination of death with return of any brain function, including consciousness, brainstem reflexes, or ventilatory effort," according to their 2019 statement.

The only jurisdiction with laws that specifically defer to these standards, however, is Nevada. The vagueness of most states' laws has contributed to divergent legal interpretations and idiosyncratic standards for determining brain death, according to the statement.

"The AAN believes that a specific, uniform standard for the determination of brain death is critically important to provide the highest quality patient-centered neurologic and end-of-life care," said James Russell, DO, MS, a neurologist at Lahey Hospital and Medical Center in Burlington, Massachusetts, and lead author of the position statement. "The AAN supports the development of legislation in every state modeled after the Nevada statute, which specifically defers to these current adult and pediatric brain death guidelines and any future updates."

> **The AAN position statement provides neurologists with guidance for responding to requests for accommodation.**

In addition to uniform institutional policies for determining brain death within U.S. medical facilities, the AAN calls for the development of training programs and credentialing mechanisms for physicians who determine brain death, regardless of their specialties. The association also supports research that enhances understanding of brain death and improved professional and public education.

While expressing respect and sympathy for requests for limited accommodation, the AAN asserts that these requests "must be based on the values of the patient, and not those of loved ones or other surrogate decision makers." The association further observes that physicians have no ethical obligation to provide medical treatment to a deceased patient. New Jersey is the only state that legally obliges physicians to provide indefinite accommodation and continued application of organ-sustaining technology.

"The AAN believes that its members have both the moral authority and professional responsibility, when lawful, to perform a brain death evaluation, including apnea testing, after informing a patient's loved ones or lawful surrogates of that intention, but without obligation to obtain informed consent," according to the statement. "This position is analogous to the authority and responsibility historically granted to the medical profession to determine circulatory death without the requirement for additional informed consent."

If a dispute about indefinite accommodation cannot be resolved, it is acceptable for a physician to withdraw organ-sustaining technology unilaterally over the objection of loved ones when legally permitted, according to the AAN. Such unilateral action is a measure of last resort and does not apply when the patient is a pregnant woman, said the authors. In the latter case, the ethical analysis should focus mainly on the welfare of the fetus.

The AAN provided financial support for the Brain Death Working Group's efforts. The statement's authors reported no relevant disclosures. The American Neurological Association and the Child Neurology Society have endorsed the AAN's position statement. **NR**

—Erik Greb

Suggested Reading

Russell JA, Epstein LG, Greer DM, et al. Brain death, the determination of brain death, and member guidance for brain death accomodation requests. *Neurology*. 2019 Jan. 2 [Epub ahead of print].

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DMTs and stem cell transplants reduce disease progression in MS

First- and second-line therapies reduce the risk of conversion to secondary progressive MS, and stem cell treatment delays disease progression.

Disease-modifying therapies (DMTs) give patients with relapsing-remitting multiple sclerosis (MS) a lower risk of developing secondary progressive disease, and risk is further reduced in specific patients with highly active disease who use nonmyeloablative hematopoietic stem cell transplantation (HSCT), according to findings from two studies published online Jan. 15 in *JAMA*.

The first study found that interferon-beta, glatiramer acetate, fingolimod, natalizumab, and alemtuzumab are associated with a lower risk of conversion to secondary progressive MS, compared with no treatment. Initial treatment with the newer therapies provided a greater risk reduction, compared with initial treatment with interferon-beta or glatiramer acetate.

The second study, described as "the first randomized trial of nonmyeloablative HSCT in patients with relapsing-remitting MS," suggests that HSCT prolongs the time to disease progression, compared with DMTs. It also suggests that HSCT can lead to clinical improvement.

DMTs reduced risk of conversion to secondary progressive MS

Few previous studies have examined the association between DMTs and the risk of conversion from relapsing-remitting MS to secondary progressive MS. Those that have analyzed this association have not used a validated definition of secondary progressive MS. J. William L. Brown, MD, of the University of Cambridge, United Kingdom, and his colleagues used a validated definition of secondary progressive MS that was published in 2016 to investigate how DMTs affect the rate of conversion, compared with no treatment. The researchers also compared the risk reduction provided by fingolimod, alemtuzumab, or natalizumab with that provided by interferon-beta or glatiramer acetate.

Dr. Brown and his colleagues analyzed prospectively collected clinical data from an international observational cohort study called MSBase. Eligible participants had relapsing-remitting MS, the complete MSBase minimum data set, at least one Expanded Disability Status Scale (EDSS) score recorded within 6 months before baseline, and at least two EDSS scores recorded after baseline. Participants initiated a DMT or began clinical monitoring during 1988–2012. The population had a minimum follow-up duration of 4 years. Patients who stopped their initial therapy within 6 months and those participating in clinical trials were excluded.

The primary outcome was conversion to secondary progressive MS. Dr. Brown and his colleagues defined this outcome as an EDSS increase of 1 point for participants with a baseline EDSS score of 5.5 or less and as an increase of 0.5 points for participants with a baseline EDSS score higher than 5.5. This increase had to occur in the absence of relapses and be confirmed at a subsequent visit 3 or fewer months later. In addition, the increased EDSS score had to be 4 or more.

After excluding ineligible participants, the investigators matched 1,555 patients from 68 centers in 21 countries. Each therapy analyzed was associated with reduced risk of converting to secondary progressive MS, compared with no treatment. The hazard ratios for conversion were 0.71 for interferon-beta or glatiramer acetate, 0.37 for fingolimod, 0.61 for natalizumab, and 0.52 for alemtuzumab, compared with no treatment.

Treatment with interferon-beta or glatiramer acetate within 5 years of disease onset was associated with a reduced risk of conversion (HR, 0.77), compared with treatment later than 5 years after disease onset. Similarly, patients who escalated treatment from interferon-beta or glatiramer acetate to any of the other three DMTs within 5 years of disease onset had a significantly lower risk of conversion (HR, 0.76) than did those who escalated later. Furthermore, initial treatment with fingolimod, alemtuzumab, or natalizumab was associated with a significantly reduced risk of conversion (HR, 0.66), compared with initial treatment with interferon-beta or glatiramer acetate.

One of the study's limitations is its observational design, which precludes the determination of causality, Dr. Brown and his colleagues said. In addition, functional score subcomponents of the EDSS were unavailable, which prevented the researchers from using the definition of secondary progressive MS with the best combination of sensitivity, specificity, and accuracy. Some analyses were limited by small numbers of patients, and the study did not evaluate the risks associated with DMTs. Nevertheless, "these findings, considered along with these therapies' risks, may help inform decisions about DMT selection," the authors concluded.

Financial support for this study was provided by the National Health and Medical Research Council of Australia and the University of Melbourne. Dr. Brown received a Next Generation Fellowship funded by the Grand Charity of the Freemasons and an MSBase 2017 Fellowship. Alemtuzumab studies conducted in Cambridge were supported by the National Institute for Health Research Cambridge Biomedical Research Centre and the MS Society UK.

HSCT delayed disease progression

In a previous case series, Richard K. Burt, MD, of Northwestern University in Chicago, and his colleagues found that patients with relapsing-remitting MS who underwent nonmyeloablative HSCT had neurologic improvement and a 70% likelihood of having a 4-year period of disease

Patients with MS who underwent nonmyeloablative HSCT had neurologic improvement

remission. Dr. Burt and his colleagues undertook the MS international stem cell transplant trial to compare the effects of nonmyeloablative HSCT with those of continued DMT treatment on disease progression in participants with highly active relapsing-remitting MS.

The researchers enrolled 110 participants at four international centers into their open-label trial. Eligible participants had two or more clinical relapses or one relapse and at least one gadolinium-enhancing lesion at a separate time within the previous 12 months, despite DMT treatment. The investigators also required participants to have an EDSS score between 2.0 and 6.0. Patients with primary or secondary progressive MS were excluded.

Dr. Burt and his colleagues randomized participants to receive HSCT or an approved DMT that was more effective or in a different class than the one they were receiving at baseline. Ocrelizumab was not administered during the study because it had not yet been approved. The investigators excluded alemtuzumab because of its association with persistent lymphopenia and autoimmune disorders. After 1 year of treatment, patients receiving a DMT who had disability progression could cross over to the HSCT arm. Patients randomized to HSCT stopped taking their usual DMT.

Time to disease progression was the study's primary end point. The investigators defined disease progression as an increase in EDSS score of at least 1 point on two evaluations 6 months apart after at least 1 year of treatment. The increase was required to result from MS. The neurologist who recorded participants' EDSS evaluations was blinded to treatment group assignment.

The researchers randomized 55 patients to each study arm. Approximately 66% of participants were women, and the sample's mean age was 36 years. There were no significant baseline differences between groups on demographic, clinical, or imaging characteristics. Three patients in the HSCT group were withdrawn from the study, and four in the DMT group were lost to follow-up after seeking HSCT at outside facilities.

Three patients in the HSCT group and 34 patients in the DMT group had disease progression. Mean follow-up duration was 2.8 years. The investigators could not calculate the median time to progression in the HSCT group because too few events occurred. Median time to progression was 24 months in the DMT group (HR, 0.07). During the first year, mean EDSS scores decreased (indicating improvement) from 3.38 to 2.36 in the HSCT group. Mean EDSS scores increased from 3.31 to 3.98 in the DMT group. No participants died, and no patients who received HSCT developed nonhematopoietic grade 4 toxicities.

"To our knowledge, this is the first randomized trial of HSCT in patients with relapsing-remitting MS," Dr. Burt and his colleagues said. Although observational studies have found similar EDSS improvements following HSCT, "this degree of improvement has not

Researchers conduct the first randomized trial of HSCT in patients with relapsing-remitting MS

been demonstrated in pharmaceutical trials even with more intensive DMT such as alemtuzumab," they concluded.

The Danhakl Family Foundation, the Cumming Foundation, the McNamara Purcell Foundation, Morgan Stanley, and the National Institute for Health Research Sheffield Clinical Research Facility provided financial support for this study. No pharmaceutical companies supported the study.

Although effective, DMTs and HSCT entail risks

The study by Brown et al. provides evidence that DMTs slow the appearance of persistent disabilities in patients with MS, Harold Atkins, MD, wrote in an accompanying editorial. Although DMTs may suppress clinical signs of disease activity for long periods in some patients, these therapies slow MS rather than halt it. DMTs require long-term administration and may cause intolerable side effects that impair patients' quality of life. Furthermore, these therapies also may result in complications such as severe depression or progressive multifocal leukoencephalopathy.

"The study by Burt et al. ... provides a rigorous indication that HSCT can be an effective treatment for selected patients with MS," Dr. Atkins said.

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Acute Myopia and Secondary Angle Closure Glaucoma A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating topiramate therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of TROKENDI XR as rapidly as possible, according to the judgment of the treating physician. Other measures, in conjunction with discontinuation of TROKENDI XR, may be helpful. Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequelae including permanent vision loss. **Visual Field Defects** Visual field defects (independent of elevated intraocular pressure) have been reported in clinical trials and in postmarketing experience in patients receiving topiramate. In clinical trials, most of these events were reversible after topiramate discontinuation. If visual problems occur at any time during treatment with TROKENDI XR, consideration should be given to discontinuing the drug. **Oligohydrosis and Hyperthermia** Oligohydrosis (decreased sweating), resulting in hospitalization in some cases, has been reported in association with topiramate use. Decreased sweating and an elevation in body temperature above normal characterized these cases. Some of the cases were reported after exposure to elevated environmental temperatures. The majority of the reports have been in pediatric patients. Patients, especially pediatric patients, treated with TROKENDI XR should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when TROKENDI XR is given with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity. **Metabolic Acidosis** TROKENDI XR can cause hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis). This metabolic acidosis is caused by renal bicarbonate loss due to carbonic anhydrase inhibition by TROKENDI XR. TROKENDI XR-induced metabolic acidosis can occur at any time during treatment. Bicarbonate decrements are usually mild to moderate (average decrease of 4 mEq/L at daily doses of 400 mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to values below 10 mEq/L. Conditions or therapies that predispose patients to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, ketogenic diet or specific drugs) may be additive to the bicarbonate lowering effects of TROKENDI XR. Metabolic acidosis was commonly observed in adult and pediatric patients treated with immediate-release topiramate in clinical trials. Manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients may also reduce growth rates, which may decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated in long-term, placebo-controlled trials. Reductions in length and weight were correlated to the degree of acidosis. TROKENDI XR treatment that causes metabolic acidosis during pregnancy can possibly produce adverse effects on the fetus and might also cause metabolic acidosis in the neonate from possible transfer of topiramate to the fetus. Measurement of Serum Bicarbonate in Epilepsy and Migraine Patients Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing TROKENDI XR (using dose tapering). If the decision is made to continue patients on TROKENDI XR in the face of persistent acidosis, alkali treatment should be considered. **Interaction with Alcohol** *In vitro* data show that, in the presence of alcohol, the pattern of topiramate release from TROKENDI XR capsules is significantly altered. As a result, plasma levels of topiramate with TROKENDI XR may be markedly higher soon after dosing and subtherapeutic later in the day. Therefore, alcohol use should be completely avoided within 6 hours prior to and 6 hours after TROKENDI XR administration. **Suicidal Behavior and Ideation** Antiepileptic drugs (AEDs) increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED, including TROKENDI XR for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Pooled analyses of 199 placebo-controlled clinical trials (mono-and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed. A pooled analysis of data for multiple AEDs determined absolute and relative risk by indication. For every 1,000 patients, the absolute risk for placebo vs drug patients was 1.0 v 3.4 (epilepsy), 5.7 v 8.5 (psychiatric), and 1.0 v 1.8 (other) for a total risk of 2.4 v 4.3. The relative risk for drug patients compared to placebo was 3.5 (epilepsy), 1.5 (psychiatric), and 1.9 (other) for a total relative risk of 1.8. The difference in risk (additional drug patients with events per 1,000 patients) was 2.4 (epilepsy), 2.9 (psychiatric), and 0.9 (other) for a total risk difference of 1.9. The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications. Anyone considering prescribing TROKENDI XR or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. **Cognitive/Neuropsychiatric Adverse Reactions** Immediate-release topiramate can cause, and therefore expected to be caused by TROKENDI XR, cognitive/neuropsychiatric adverse reactions. The most frequent of these can be classified into three general categories: 1) Cognitive-related dysfunction (e.g., confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, particularly word-finding difficulties); 2) Psychiatric/behavioral disturbances (e.g., depression or mood problems); and 3) Somnolence or fatigue. Adult Patients *Cognitive-Related Dysfunction*-Rapid titration rate and higher initial dose were associated with higher incidences of cognitive-related dysfunction. In the 6-month migraine prophylaxis controlled trials of immediate-release topiramate using a slower titration regimen (25 mg per day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse reactions was 19% for topiramate 50 mg per day, 22% for 100 mg per day (the recommended dose), 28% for 200 mg per day and 10% for placebo. Cognitive adverse reactions most commonly developed during titration and sometimes persisted after completion of titration. *Psychiatric/Behavioral Disturbances*-Psychiatric/behavioral disturbances (e.g., depression, mood) were dose-related for both the adjunctive epilepsy and migraine populations treated with topiramate. *Somnolence/Fatigue*-For the migraine population, the incidences of both somnolence and fatigue were dose-related and more common in the titration phase. Pediatric Patients In pediatric migraine patients, the incidence of cognitive/neuropsychiatric adverse reactions was increased in immediate-release topiramate-treated patients compared to placebo. The risk for cognitive/neuropsychiatric adverse reactions was dose-dependent, and was greatest at the highest dose (200 mg). This risk for cognitive/neuropsychiatric adverse reactions was also greater in younger patients (6 to 11 years of age) than in older patients (12 to 17 years of age). The most common cognitive/neuropsychiatric adverse reaction in these trials was difficulty with concentration/attention. Cognitive adverse reactions most commonly developed during titration and sometimes persisted for various durations after completion of titration. The Cambridge Neuropsychological Test Automated Battery (CANTAB) was administered to adolescents (12 to 17 years of age) to assess the effects of topiramate on cognitive function at baseline at the end of the Study 3. Mean change from baseline in certain CANTAB tests suggests that topiramate treatment may result in psychomotor slowing and decreased verbal fluency. **Fetal Toxicity** Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have an increased risk for cleft lip and/or cleft palate (oral clefts) and for being small for gestational age. When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring. Consider the benefits and risks of TROKENDI XR when administering the drug in women of childbearing potential, particularly when TROKENDI XR is considered for a condition not usually associated with permanent injury or death. TROKENDI XR should be used during pregnancy only if the potential benefit outweighs the potential risk. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus. **Withdrawal of Antiepileptic Drugs** In patients with or without a history of seizures or epilepsy, antiepileptic drugs, including TROKENDI XR, should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. In situations where rapid withdrawal of TROKENDI XR is medically required, appropriate monitoring is recommended. **Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid Use)** Topiramate treatment can cause hyperammonemia with or without encephalopathy. The risk for hyperammonemia with topiramate appears dose-related. Hyperammonemia has been reported more frequently when topiramate is used concomitantly with valproic acid. Postmarketing cases of hyperammonemia with or without encephalopathy have been reported with topiramate and valproic acid in patients who previously tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy and/or vomiting. In most cases, hyperammonemic encephalopathy abated with discontinuation of treatment. The incidence of hyperammonemia in pediatric patients 12 to 17 years of age in migraine prophylaxis trials was 26% in patients taking topiramate monotherapy at 100 mg/day, and 14% in patients taking topiramate at 50 mg/day, compared to 9% in patients taking placebo. There was also an increased incidence of markedly increased hyperammonemia at the 100 mg dose. Dose-related hyperammonemia was also seen in pediatric patients 1 to 24 months of age treated with topiramate and concomitant valproic acid for partial onset epilepsy, and this was not due to a pharmacokinetic interaction. In some patients, hyperammonemia can be asymptomatic. **Monitoring for Hyperammonemia** Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, topiramate or TROKENDI XR treatment or an interaction of concomitant topiramate-based product and valproic acid treatment may exacerbate existing defects or unmask deficiencies in susceptible persons. In patients who develop unexplained lethargy, vomiting, or changes in mental status associated with any topiramate treatment, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. **Kidney Stones** Topiramate increases the risk of kidney stones. As in the general population, the incidence of stone formation among topiramate-treated patients was higher in men. Kidney stones have also been reported in pediatric patients taking topiramate for epilepsy or migraine. During long-term (up to 1 year) topiramate treatment in an open-label extension study of 284 pediatric patients 1-24 months old with epilepsy, 7% developed kidney or bladder stones. TROKENDI XR would be expected to have the same effect as immediate-release topiramate on the formation of kidney stones. Topiramate is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors can promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of TROKENDI XR with any other drug producing metabolic acidosis, or potentially in patients on a ketogenic diet, may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided. Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation. **Hypothermia with Concomitant Valproic Acid Use** Hypothermia, defined as a drop in body core temperature to < 35ºC (95ºF), has been reported in association with topiramate use with concomitant valproic acid (VPA) both in conjunction with and in the absence of hyperammonemia. This adverse reaction in patients using concomitant topiramate and valproate can occur after starting topiramate treatment or after increasing the daily dose of topiramate. Consideration should be given to stopping TROKENDI XR or valproate in patients who develop hypothermia, which may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma, and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.

ADVERSE REACTIONS

The data described in the following sections were obtained using immediate-release topiramate tablets. TROKENDI XR has not been studied in a randomized, placebo-controlled Phase III clinical study; however, it is expected that TROKENDI XR would produce a similar adverse reaction profile as immediate-release topiramate. **Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice. Migraine *Adults*-In the four multicenter, randomized, double-blind, placebo-controlled, parallel-group migraine prophylaxis clinical trials (which included 35 pediatric patients 12 to 15 years of age), most adverse reactions occurred more frequently during the titration period than during the maintenance period. The most common adverse reactions with immediate-release topiramate 100 mg in migraine prophylaxis clinical trials of predominantly adults that were seen at an incidence higher (≥5%) than in the placebo group were: paresthesia, anorexia, weight loss, taste perversion, diarrhea, difficulty with memory, hypoesthesia, and nausea (see Table 7, full Prescribing Information). Adverse reactions that occurred in the placebo-controlled trials where the incidence in any immediate-release topiramate group was 3%-5% and greater than placebo patients were: arthralgia, pharyngitis, anxiety, nervousness, viral infection, coughing, pruritis, urinary tract infection, blurred vision, dyspnea, bronchitis, ejaculation premature, menstrual disorder, gastroenteritis, and dry mouth. The incidence of some adverse reactions (e.g., fatigue, dizziness, somnolence, difficulty with memory, difficulty with concentration/attention) was dose-related and greater at higher than recommended topiramate dosing (200 mg/day) compared to the incidence of these adverse reactions at the recommended dosing (100 mg/day). Of the 1,135 patients exposed to immediate-release topiramate in the adult placebo-controlled studies, 25% discontinued due to adverse reactions, compared to 10% of the 445 placebo patients. The adverse reactions associated with discontinuing therapy in the immediate-release topiramate-treated patients in these studies included paresthesia (7%), fatigue (4%), nausea (4%), difficulty with concentration/attention (3%), insomnia (3%), anorexia (2%), and dizziness (2%). Patients treated in

Although effective, DMTs and HSCT still entail risks

He pointed out, however, that treating physicians have concerns about this procedure, which is resource intensive and "requires specialized medical and nursing expertise and dedicated hospital infrastructure to minimize its risks." Many patients in the study had moderate to severe acute toxicity following treatment, Dr. Atkins noted, and patient selection thus requires caution.

An important limitation of the study is that participants did not have access to alemtuzumab or ocrelizumab, which arguably are the most effective DMTs, Dr. Atkins said. The study began in 2005, when fewer DMTs were available. "The inclusion of patients who were less than optimally treated in the DMT group needs to be considered when interpreting the results of this study," Dr. Atkins said.

Furthermore, Burt and colleagues studied patients with highly active MS, but "only a small proportion of the MS patient population exhibits this degree of activity," he added. The results therefore may not be generalizable. Nevertheless, "even with the limitations of the trial, the results support a role for HSCT delivered at centers that are experienced in the clinical care of patients with highly active MS," Dr. Atkins concluded.

Dr. Atkins is affiliated with the Ottawa Hospital Blood and Marrow Transplant Program at the University of Ottawa. He reported no conflicts of interest. **NR**

—Erik Greb

these studies experienced mean percent reductions in body weight that were dose-dependent. This change was not seen in the placebo group. Mean changes of 0%, -2%, -3%, and -4% were seen for the placebo group, immediate-release topiramate 50 mg, 100 mg, and 200 mg groups, respectively. Pediatric Patients 12 to 17 Years of Age In five randomized, double-blind, placebo-controlled, parallel-group migraine prophylaxis clinical trials, most of the adverse reactions occurred more frequently during the titration period than during the maintenance period. Among adverse reactions with onset during titration, approximately half persisted into the maintenance period. In four, fixed-dose, double-blind migraine prophylaxis clinical trials in immediate-release topiramate treated pediatric patients 12 to 17 years of age, the most common adverse reactions with immediate-release topiramate 100 mg that were seen at an incidence higher (≥5%) than in the placebo group were: paresthesia, upper respiratory tract infection, anorexia, and abdominal pain (see Table 8, full Prescribing Information). Adverse reactions in pediatric patients in controlled migraine trials when the incidence in an immediate-release topiramate dose group was at least 5% or higher and greater than the incidence of placebo were: insomnia, sinusitis, nausea, viral infection, coughing, conjunctivitis, rhinitis, weight loss, and dizziness. Many adverse reactions indicate a dose-dependent relationship. The incidence of some adverse reactions (e.g., allergy, fatigue, headache, anorexia, insomnia, somnolence, and viral infection) was dose-related and greater at higher than recommended immediate-release topiramate dosing (200 mg daily) compared to the incidence of these adverse reactions at the recommended dosing (100 mg daily). In the double-blind placebo-controlled studies, adverse reactions led to discontinuation of treatment in 8% of placebo patients compared with 6% of immediate-release topiramate-treated patients. Adverse reactions associated with discontinuing therapy that occurred in more than one immediate-release topiramate-treated patient were fatigue (1%), headache (1%), and somnolence (1%). Increased Risk for Bleeding Topiramate is associated with an increased risk for bleeding. In a pooled analysis of placebo-controlled studies of approved and unapproved indications, bleeding was more frequently reported as an adverse reaction for topiramate than for placebo (4.5% versus 3.0% in adult patients, and 4.4% versus 2.3% in pediatric patients). In this analysis, the incidence of serious bleeding events for topiramate and placebo was 0.3% versus 0.2% for adult patients, and 0.4% versus 0% for pediatric patients. Adverse bleeding reactions reported with topiramate ranged from mild epistaxis, ecchymosis, and increased menstrual bleeding to life-threatening hemorrhages. In patients with serious bleeding events, conditions that increased the risk for bleeding were often present, or patients were often taking drugs that cause thrombocytopenia (other antiepileptic drugs) or affect platelet function or coagulation (e.g., aspirin, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, or warfarin or other anticoagulants). Other Adverse Reactions Observed During Clinical Trials Other adverse reactions seen during clinical trials were: abnormal coordination, eosinophilia, gingival bleeding, hematuria, hypotension, myalgia, myopia, postural hypotension, scotoma, suicide attempt, syncope, and visual field defect. Laboratory Test Abnormalities *Adult Patients*-In addition to changes in serum bicarbonate (i.e., metabolic acidosis), sodium chloride and ammonia, immediate-release topiramate was associated with changes in several clinical laboratory analytes in randomized, double-blind, placebo-controlled studies. *Pediatric Patients*-In pediatric patients (ranging from 6-17 years old) receiving immediate-release topiramate for migraine prophylaxis, there was an increased incidence for an increased result (relative to normal analyte reference range) associated with immediate-release topiramate (vs placebo) for the following clinical laboratory analytes: creatinine, BUN, uric acid, chloride, ammonia, alkaline phosphatase, total protein, platelets, and eosinophils. The incidence was also increased for a decreased result for phosphorus, bicarbonate, total white blood count, and neutrophils. TROKENDI XR is not indicated for prophylaxis of migraine headache in pediatric patients less than 12 years of age. **Postmarketing Experience** The following adverse reactions have been identified during post-approval use of immediate-release topiramate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Body as a Whole-General Disorders: oligohydrosis and hyperthermia, hyperammonemia, hyperammonemic encephalopathy, hypothermia with concomitant valproic acid Gastrointestinal System Disorders: hepatic failure (including fatalities), hepatitis, pancreatitis Skin and Appendage Disorders: bullous skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), pemphigus Urinary System Disorders: kidney stones Vision disorders: acute myopia, secondary angle closure glaucoma, maculopathy

DRUG INTERACTIONS

Alcohol Alcohol use is contraindicated within 6 hours prior to and 6 hours after TROKENDI XR administration. **Antiepileptic Drugs** Concomitant administration of phenytoin or carbamazepine with topiramate resulted in a clinically significant decrease in plasma concentrations of topiramate when compared to topiramate given alone. A dosage adjustment may be needed. Concomitant administration of valproic acid and topiramate has been associated with hypothermia and hyperammonemia with and without encephalopathy. Examine blood ammonia levels in patients in whom the onset of hypothermia has been reported. **Other Carbonic Anhydrase Inhibitors** Concomitant use of topiramate, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., zonisamide, acetazolamide, or dichlorphenamide), may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Patients should be monitored for the appearance or worsening of metabolic acidosis when TROKENDI XR is given concomitantly with another carbonic anhydrase inhibitor. **CNS Depressants** Concomitant administration of topiramate with other CNS depressant drugs or alcohol has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse reactions, TROKENDI XR should be used with extreme caution if used in combination with alcohol and other CNS depressants. **Oral Contraceptives** The possibility of decreased contraceptive efficacy and increased breakthrough bleeding may occur in patients taking combination oral contraceptive products with TROKENDI XR. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding. **Hydrochlorothiazide (HCTZ)** Topiramate C_{max} and AUC increased when HCTZ was added to immediate-release topiramate. The clinical significance of this change is unknown. The addition of HCTZ to TROKENDI XR may require a decrease in the TROKENDI XR dose. **Pioglitazone** A decrease in the exposure of pioglitazone and its active metabolites were noted with the concurrent use of pioglitazone and immediate-release topiramate in a clinical trial. The clinical relevance of these observations is unknown; however, when TROKENDI XR is added to pioglitazone therapy or pioglitazone is added to TROKENDI XR therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state. **Lithium** An increase in systemic exposure of lithium following topiramate doses of up to 600 mg/day can occur. Lithium levels should be monitored when co-administered with high-dose TROKENDI XR. **Amitriptyline** Some patients may experience a large increase in amitriptyline concentration in the presence of TROKENDI XR and any adjustments in amitriptyline dose should be made according to the patients' clinical response and not on the basis of plasma levels.

USE IN SPECIFIC POPULATIONS

Pregnancy ***Pregnancy Exposure Registry***-There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to topiramate during pregnancy. Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll-free number 1-888-233-2334. Information about the North American Drug Pregnancy Registry can be found at http://www.aedpregnancyregistry.org/. ***Risk Summary***-Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have increased risk for cleft lip and/or cleft palate (oral clefts) and for being small for gestational age [see Human Data]. In multiple animal species, topiramate demonstrated developmental toxicity, including teratogenicity, in the absence of maternal toxicity at clinically relevant doses [see Animal Data]. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. ***Clinical Considerations***-Fetal/Neonatal Adverse Reactions-Consider the benefits and risks of topiramate when prescribing this drug to women of childbearing potential, particularly when topiramate is considered for a condition not usually associated with permanent injury or death. Because of the risk of oral clefts to the fetus, which occur in the first trimester of pregnancy before many women know they are pregnant, all women of childbearing potential should be informed of the potential risk to the fetus from exposure to topiramate. Women who are planning a pregnancy should be counseled regarding the relative risks and benefits of topiramate use during pregnancy, and alternative therapeutic options should be considered for these patients. Labor or Delivery-Although the effect of topiramate on labor and delivery in humans has not been established, the development of topiramate-induced metabolic acidosis in the mother and/or in the fetus might affect the fetus' ability to tolerate labor. TROKENDI XR treatment can cause metabolic acidosis. The effect of topiramate-induced metabolic acidosis has not been studied in pregnancy; however, metabolic acidosis in pregnancy (due to other causes) can cause decreased fetal growth, decreased fetal oxygenation, and fetal death, and may affect the fetus' ability to tolerate labor. Pregnant patients should be monitored for metabolic acidosis and treated as in the nonpregnant state. Newborns of mothers treated with TROKENDI XR should be monitored for metabolic acidosis because of transfer of topiramate to the fetus and possible occurrence of transient metabolic acidosis following birth. ***Data***-Human Data-Data from pregnancy registries indicate an increased risk of oral clefts in infants exposed to topiramate during the first trimester of pregnancy. In the NAAED pregnancy registry, the prevalence of oral clefts among topiramate-exposed infants (1.1%) was higher than the prevalence of infants exposed to reference AEDs (0.36%), or the prevalence in infants of mothers without epilepsy and without exposure to AEDs (0.12%). It was also higher than the background prevalence in United States (0.17%) as estimated by the Centers for Disease Control and Prevention (CDC). The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 9.6 (95% Confidence Interval=[CI] 4.0-23.0) as compared to the risk in a background population of untreated women. The UK Epilepsy and Pregnancy Register reported a prevalence of oral clefts among infants exposed to topiramate monotherapy (3.2%) that was 16 times higher than the background rate in the UK (0.2%). Data from the NAAED pregnancy registry and a population-based birth registry cohort indicate that exposure to topiramate *in utero* is associated with an increased risk of small for gestational age (SGA) newborns (birth weight <10th percentile). In the NAAED pregnancy registry, 18% of topiramate-exposed newborns were SGA compared to 7% of newborns exposed to a reference AED, and 5% of newborns of mothers without epilepsy and without AED exposure. In the Medical Birth Registry of Norway (MBRN), a population-based pregnancy registry, 25% of newborns in the topiramate monotherapy exposure group were SGA compared to 9% in the comparison group who were unexposed to AEDs. The long-term consequences of the SGA findings are not known. **Lactation** ***Risk Summary***-Topiramate is excreted in human milk [see Data]. The effects of topiramate exposure in breastfed infants or on milk production are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TROKENDI XR and any potential adverse effects on the breastfed infant from TROKENDI XR or from the underlying maternal condition. ***Data***-Limited data from 5 women with epilepsy treated with topiramate during lactation showed drug levels in milk similar to those in maternal plasma. **Females and Males of Reproductive Potential** *Contraception*-Women of childbearing potential who are not planning a pregnancy should use effective contraception because of the risks to the fetus of oral clefts and of being small for gestational age. **Pediatric Use** Because the capsule must be swallowed whole, and may not be sprinkled on food, crushed, or chewed, TROKENDI XR is recommended only for children age 6 or older. Migraine Prophylaxis in Pediatric Patients 12 to 17 Years of Age-Safety and effectiveness of topiramate in the prophylaxis of migraine was studied in 5 double-blind, randomized, placebo-controlled, parallel-group trials in a total of 219 pediatric patients, at doses of 50 mg/day to 200 mg/day, or 2 to 3 mg/kg/day. These comprised a fixed dose study in 103 pediatric patients 12 to 17 years of age, a flexible dose (2 to 3 mg/kg/day), placebo-controlled study in 157 pediatric patients 6 to 16 years of age (including 67 pediatric patients 12 to 16 years of age), and a total of 49 pediatric patients 12 to 17 years of age in 3 studies of migraine prophylaxis primarily in adults. Open-label extension phases of 3 studies enabled evaluation of long-term safety for up to 6 months after the end of the double-blind phase. Efficacy of topiramate (2 to 3 mg/kg/day) for migraine prophylaxis was not demonstrated in a placebo-controlled trial of 157 pediatric patients (6 to 16 years of age) that included treatment of 67 pediatric patients (12 to 16 years of age) for 20 weeks. In the pediatric trials (12 to 17 years of age) in which patients were randomized to placebo or a fixed daily dose of immediate-release topiramate, the most common adverse reactions with immediate-release topiramate that were seen at an incidence higher (≥5%) than in the placebo group were: paresthesia, upper respiratory tract infection, anorexia, and abdominal pain. The most common cognitive adverse reaction in pooled double-blind studies in pediatric patients 12 to 17 years of age was difficulty with concentration/attention. Markedly abnormally low serum bicarbonate values indicative of metabolic acidosis were reported in topiramate-treated pediatric migraine patients. In topiramate-treated pediatric patients (12 to 17 years of age) compared to placebo-treated patients, abnormally increased results were more frequent for creatinine, BUN, uric acid, chloride, ammonia, total protein, and platelets. Abnormally decreased results were observed with topiramate vs placebo treatment for phosphorus and bicarbonate. Notable changes (increases and decreases) from baseline in systolic blood pressure, diastolic blood pressure, and pulse that were observed occurred more commonly in pediatric patients treated with topiramate compared to pediatric patients treated with placebo. Migraine Prophylaxis in Pediatric Patients 6 to 11 Years of Age-Safety and effectiveness in pediatric patients below the age of 12 years have not been established for the prophylaxis treatment of migraine headache. In a double-blind study in 90 pediatric patients 6 to 11 years of age (including 59 topiramate-treated and 31 placebo patients), the adverse reaction profile was generally similar to that seen in pooled double-blind studies of pediatric patients 12 to 17 years of age. The most common adverse reactions that occurred in immediate-release topiramate-treated pediatric patients 6 to 11 years of age, and at least twice as frequently than placebo, were gastroenteritis (12% topiramate, 6% placebo), sinusitis (10% topiramate, 3% placebo), weight loss (8% topiramate, 3% placebo) and paresthesia (7% topiramate, 0% placebo). Difficulty with concentration/attention occurred in 3 topiramate-treated patients (5%) and 0 placebo-treated patients. The risk for cognitive adverse reactions was greater in younger patients (6 to 11 years of age) than in older patients (12 to 17 years of age). **Geriatric Use** Clinical studies of immediate-release topiramate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Dosage adjustment may be necessary for elderly with creatinine clearance less than 70 mL/min/1.73 m^2. Estimate GFR should be measured prior to dosing. **Renal Impairment** The clearance of topiramate is reduced in patients with moderate (creatinine clearance 30 to 69 mL/min/1.73m^2) and severe (creatinine clearance less than 30 mL/min/1.73m^2) renal impairment. A dosage adjustment is recommended in patients with moderate or severe renal impairment. **Patients Undergoing Hemodialysis** Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than in a normal individual. A dosage adjustment may be required.

OVERDOSAGE

Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbance, blurred vision, diplopia, impaired mentation, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness, and depression. The clinical consequences were not severe in most cases, but deaths have been reported after overdoses involving topiramate. Topiramate overdose has resulted in severe metabolic acidosis. A patient who ingested a dose of immediate-release topiramate between 96 g and 110 g was admitted to hospital with coma lasting 20 to 24 hours followed by full recovery after 3 to 4 days. Similar signs, symptoms, and clinical consequences are expected to occur with overdosage of TROKENDI XR. Therefore, in acute TROKENDI XR overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to absorb topiramate *in vitro*. Hemodialysis is an effective means of removing topiramate from the body. **Pharmacokinetics** Specific Populations-*Hepatic Impairment*-Plasma clearance of topiramate decreased a mean of 26% in patients with moderate to severe hepatic impairment.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Manufactured for: Supernus Pharmaceuticals, Inc., Rockville, Maryland 20850

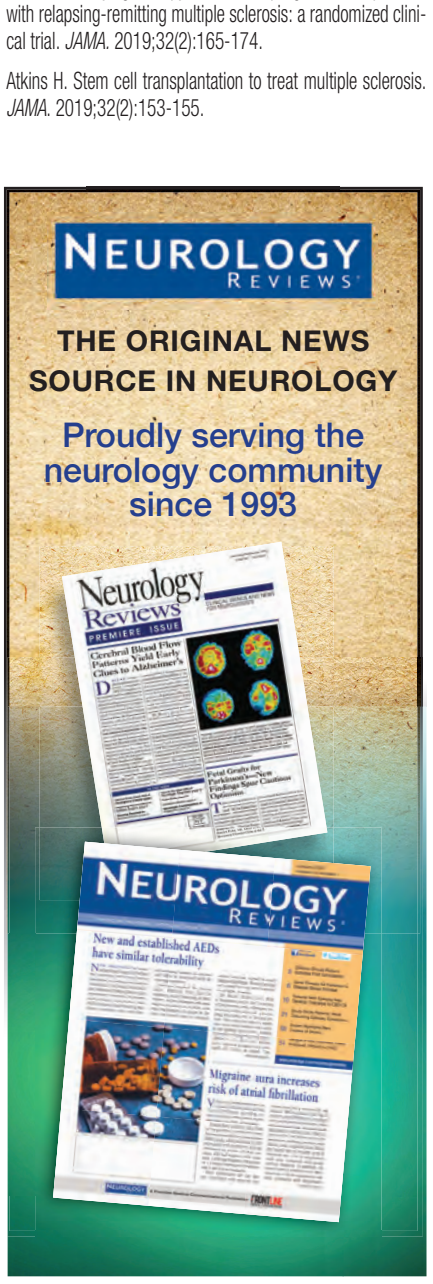
RA-TRO-BS-HCP-V3 Revised: June 2018 Based on PI Jan 2018

Suggested Reading

Brown JWL, Coles A, Horakova D, et al. Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. *JAMA*. 2019;32(2):175-187.

Burt RK, Balabanov R, Burman J, et al. Effect of nonmyeloblative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis: a randomized clinical trial. *JAMA*. 2019;32(2):165-174.

Atkins H. Stem cell transplantation to treat multiple sclerosis. *JAMA*. 2019;32(2):153-155.



Daclizumab beta may be superior to interferon beta on MS disability progression

A post hoc analysis indicates that daclizumab beta has superior efficacy, compared with interferon beta-1a, regardless of patients' baseline characteristics.

Daclizumab beta has benefits over interferon beta-1a on measures of disability and function in patients with relapsing-remitting multiple sclerosis (MS), according to research published in the December 2018 issue of the *Multiple Sclerosis Journal*. The benefits are observed in the overall patient population, as well as in subgroups of patients based on demographic and disease characteristics.

The phase 3 DECIDE study compared the safety and efficacy of subcutaneous daclizumab beta (150 mg) every 4 weeks with those of intramuscular interferon beta-1a (30 µg) once weekly in patients with relapsing-remitting MS. Daclizumab beta reduced the risk of 24-week confirmed disability progression, as assessed by the Expanded Disability Status Scale (EDSS), by 27%, compared with interferon beta-1a. Daclizumab beta also

> **Daclizumab beta was associated with a lower risk of 24-week confirmed disability progression in all subgroups.**

was associated with a greater median change from baseline to week 96 in MS Functional Composite (MSFC) score and a 24% reduction in the risk of clinically meaningful worsening on the physical impact subscale of the patient-reported 29-Item MS Impact Scale (MSIS-29 PHYS).

To shed light on the treatment's effects in various demographic groups and in patients with specific clinical characteristics, Stanley L. Cohan, MD, PhD, medical director of Providence MS Center in Portland, Oregon, and colleagues conducted a post hoc analysis of DECIDE data. They examined the treatment effects of daclizumab beta and interferon beta-1a on patient disability or impairment in specific patient subgroups. The investigators examined results according to demographic characteristics, such as age (that is, 35 years or younger and older than 35 years) and sex. They also examined results in subgroups with the following baseline disease characteristics: disability (as defined by EDSS score), relapses in the previous 12 months, disease duration, presence of gadolinium-enhancing lesions, T2 hyperintense lesion volume, disease activity, prior use of disease-modifying treatment, and prior use of interferon beta.

Dr. Cohan and colleagues focused on the following three outcome measures: 24-week confirmed disability progression (as measured by EDSS), 24-week sustained worsening on the MSFC, and the proportion of patients with clinically meaningful worsening in MSIS-29 PHYS at week 96. The researchers defined 24-week confirmed disability progression as an increase in the EDSS score of one or more points from a baseline score of 1 or higher, or 1.5 points or more from a baseline score of 0, as confirmed after 24 weeks. They defined 24-week sustained worsening on the MSFC as worsening of 20% or more on the Timed 25-Foot Walk, worsening of 20% or more on the Nine-Hole Peg Test, or a decrease of 4 or more points on the Symbol Digit Modalities Test sustained for 24 weeks.

Of the 1,841 patients enrolled in DECIDE, 922 were randomized to interferon beta-1a, and 919 were randomized to daclizumab beta. The treatment groups were well balanced in terms of demographic characteristics. Patients' mean age was approximately 36 years, 68% of participants were female, and 90% of patients were white. Mean time since diagnosis at baseline was about 4 years, mean number of relapses in the previous year was 1.6, and mean baseline EDSS score was 2.5.

Daclizumab beta was associated with a lower risk of 24-week confirmed disability progression, compared with interferon beta-1a, in all subgroups. Patients aged 35 years or younger had the greatest risk reduction.

The proportion of patients who had 24-week sustained worsening on the MSFC at week 96 was 24% for daclizumab beta and 28% for interferon beta-1a. In the whole study population, daclizumab beta reduced the risk of this outcome by 20%, compared with interferon beta-1a. Daclizumab beta resulted in improved outcomes among all subgroups, compared with interferon beta-1a.

In addition, daclizumab beta reduced the risk of a clinically meaningful worsening of MSIS-29 PHYS at week 96 by 24%, compared with interferon beta-1a. The investigators observed trends favoring daclizumab beta in all subgroups.

"These analyses should be interpreted as exploratory and hypothesis-generating for future studies," said Dr. Cohan and colleagues. They observed that some of the subgroups analyzed had small sample sizes and that no adjustments were made for multiple testing. Nevertheless, the results suggest that daclizumab beta has superior efficacy, compared with interferon beta-1a, regardless of patients' demographic and disease characteristics, they concluded.

Biogen and AbbVie Biotherapeutics supported the study. **NR**

—Erik Greb

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Cohan SL, Kappos L, Giovannoni G, et al. Efficacy of daclizumab beta versus intramuscular interferon beta-1a on disability progression across patient demographic and disease activity subgroups in DECIDE. *Mult Scler J*. 2018;24(14):1883-1891.

NEWSROUNDUP

How does alcohol consumption affect risk of AF?

Regular moderate alcohol consumption, a modifiable risk factor for atrial fibrillation (AF), is associated with lower atrial voltage and conduction slowing, according to research published online Jan. 9 in *HeartRhythm*. Before AF ablation, 75 patients underwent high-density left atrial mapping. Investigators classified the patients as lifelong nondrinkers, mild drinkers (2–7 drinks/week), or moderate drinkers (8–21 drinks/week). Compared with nondrinkers, moderate drinkers had significantly lower mean global bipolar voltages, slower conduction velocity, and a higher proportion of complex atrial potentials. In mild drinkers, global complex potentials and regional low-voltage zones in the septum and lateral wall were increased.

Drug may improve social gaze in fragile X syndrome

Mavoglurant may improve eye gaze behavior and alter sympathetically driven reactivity to faces in patients with fragile X syndrome, according to a study published Jan. 17 in *PLoS One*. Researchers examined social gaze behavior in 57 patients with fragile X syndrome at baseline and after 3 months of blinded treatment with one of three doses of mavoglurant or placebo. Patients who received mavoglurant demonstrated increased total absolute looking time and number of fixations to the eye region while viewing human faces, compared with patients who received placebo. Mavoglurant-treated patients also had greater pupil reactivity to faces.

Active migraine in women associated with lower risk of developing diabetes

The prevalence of migraine decreases in the years before diabetes diagnosis.

Women with active migraine are less likely to develop type 2 diabetes mellitus and have a decrease in migraine symptoms before a diagnosis of diabetes, indicating an inverse relationship between hyperglycemia, hyperinsulinism, and migraine, according to research published online ahead of print December 17, 2018, in *JAMA Neurology*.

"Because plasma glucose concentration rises with time up to the point of type 2 diabetes occurrence, the prevalence of migraine symptoms may decrease," said Guy Fagherazzi, PhD, of the Center for Research in Epidemiology and Population Health at the Gustave Roussy Institute in Villejuif, France, and colleagues. "Consequently, tracking the evolution and especially the decrease of migraine frequency in individuals with migraine at high risk of diabetes, such as individuals with obesity, irrespective of age, could be the sign of emerging increased blood glucose levels, prediabetes, or type 2 diabetes."

A prospective cohort study examined

The researchers examined data from the prospective Etude Epidémiologique Auprès des Femmes de la Mutuelle Générale de l'Education Nationale (E3N) study, which was initiated in 1990, and identified 74,247 women (mean age, 61 years) who had provided information about migraine history in a 2002 follow-up questionnaire and had 10-year follow-up data during 2004–2014. The women in the cohort were born during 1925–1950 and completed periodic questionnaires about their health, including migraine status and medications, beginning in 1992. The participants were divided into groups with no migraine (49,199 participants), active migraine (7,839 participants), or prior migraine history (17,209 participants). Patients with diabetes at baseline were excluded.

Dr. Fagherazzi and his colleagues found 2,372 cases of incident type 2 diabetes during the follow-up period. Women with active migraine were less likely to have diabetes (hazard ratio, 0.80) than were the participants without migraine, and this inverse association was strengthened after the researchers adjusted for factors such as myocardial infarction, education level, family history of diabetes, body mass index, smoking status, hypertension, physical activity, oral contraceptive use, menopausal status, menopausal hormone therapy, handedness, antimigraine preparations, and other prescribed migraine drugs (HR, 0.70).

Among participants who developed diabetes, the researchers also found a decrease in the prevalence of active migraine from 22% to 11% in the 24 years before diabetes diagnosis, after adjusting for diabetes risk factors. Migraine prevalence subsequently remained stable at 11% for these participants for as long as 22 years.

"The linear decrease of migraine prevalence long before and the plateau long after type 2 diabetes diagnosis is novel, and the association deserves to be studied in other populations," said Dr. Fagherazzi and his colleagues. "The potential beneficial role of both hyperglycemia and hyperinsulinism on migraine occurrence needs to be further explored."

The researchers noted limitations in the study, including the identification of migraine by self-report, the exclusion of nonpharmacologically treated diabetes cases, the observational nature of the study, and the homogeneous population in the E3N study. The cohort consisted mainly of women in menopause who mostly were teachers covered by the same health insurance plan.

The reason for the association is unclear

Although it has been noted for some time in the clinical setting, researchers are still unsure why there is an inverse association between active migraine and type 2 diabetes mellitus, as noted by Fagherazzi et al. in a recent study, said Amy A. Gelfand, MD, a pediatric neurologist and headache specialist at the University of California, San Francisco Benioff Children's Hospital, and Elizabeth Loder, MD, MPH, chief of the division of headache and pain at Brigham and Women's Hospital in Boston, in an accompanying editorial.

One plausible explanation is the presence of calcitonin gene–related peptide in animal models of energy metabolism and in the pathophysiology of migraine. It is possible that insulin resistance and hyperglycemia damage the sensory neurons that produce the peptide. If these damaged nerves are soothed, migraine may resolve.

Besides a reduced risk of incident diabetes, other positive outcomes associated with active migraine include an increased likelihood of having a healthy cardiovascular system and decreased alcohol consumption. The epidemiology of migraine and findings like those in this study prompt the question of what migraine is good for.

The study by Fagherazzi and colleagues was funded by a grant from the French Research agency. The E3N cohort study was funded by the Mutuelle Générale de l'Education Nationale, European Community, French League against Cancer, Gustave Roussy, and the French Institute of Health and Medical Research. Drs. Gelfand and Loder disclosed financial relationships with companies that market treatments for migraine. **NR**

—Jeff Craven

Suggested Reading

Fagherazzi G, El Fatouhi D, Fournier A, et al. Associations between migraine and type 2 diabetes in women: Findings from the E3N cohort study. *JAMA Neurol.* 2018 Dec 17 [Epub ahead of print].

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NEWSROUNDUP

FDA approves generic version of vigabatrin

The Food and Drug Administration has approved the first generic version of vigabatrin (Sabril) 500-mg tablets. The drug is approved for the adjunctive treatment of focal seizures in patients aged 10 years and older who have not had an adequate response to other therapies.

The approval was granted to Teva Pharmaceuticals.

An FDA announcement noted that the agency has prioritized the approval of generic versions of drugs to improve access to treatments and to lower drug costs. Vigabatrin had been included on an FDA list of off-patent, off-exclusivity branded drugs without approved generics. The approval of generic vigabatrin "demonstrates that there is an open pathway to approving products like this one," said FDA Commissioner Scott Gottlieb, MD.

The label for vigabatrin tablets includes a boxed warning about permanent vision loss. The generic vigabatrin tablets are part of a single shared-system Risk Evaluation and Mitigation Strategy (REMS) program with other drug products containing vigabatrin.

The most common side effects associated with vigabatrin tablets include dizziness, fatigue, sleepiness, involuntary eye movement, tremor, blurred vision, memory impairment, weight gain, joint pain, upper respiratory tract infection, aggression, double vision, abnormal coordination, and a confused state. Serious side effects associated with vigabatrin tablets include permanent vision loss and risk of suicidal thoughts or actions.

Alcohol use and psychological distress are associated with possible RBD

These associations were previously unreported, and the results suggest the need for further study.

Alcohol consumption and psychological distress are associated with possible REM sleep behavior disorder (RBD), according to a population-based cohort study published in *Neurology*. The results also replicate previous findings of an association between possible RBD and smoking, low education, and male sex.

The risk factors for RBD have been studied comparatively little. "While much is still unknown about RBD, it can be caused by medications or it may be an early sign of another neurologic condition like Parkinson's disease, dementia with Lewy bodies, or multiple system atrophy," according to Ronald B. Postuma, MD, an associate professor at McGill University, Montreal. "Identifying lifestyle and personal risk factors linked to this sleep disorder may lead to finding ways to reduce the chances of developing it."

> REM sleep behavior disorder may be an early sign of a neurologic condition like Parkinson's disease.

To assess sociodemographic, socioeconomic, and clinical correlates of possible RBD, Dr. Postuma and his colleagues examined baseline data collected between 2012 and 2015 in the Canadian Longitudinal Study on Aging (CLSA), which included 30,097 participants. To screen for possible RBD, the CLSA researchers asked patients, "Have you ever been told, or suspected yourself, that you seem to 'act out your dreams' while asleep (e.g., punching, flailing your arms in the air, making running movements, etc.)?" Participants answered additional questions to rule out RBD mimics. Patients with symptom onset before age 20 years, positive apnea screen, or a diagnosis of dementia, Alzheimer's disease, parkinsonism, or Parkinson's disease were excluded from analysis.

In all, 3,271 participants screened positive for possible RBD. After the investigators excluded participants with potential mimics, 958 patients (about 3.2% of the total population) remained in the analysis. Approximately 59% of patients with possible RBD were male, compared with 42% of controls. Patients with possible RBD were more likely to be married, in a common-law relationship, or widowed.

Participants with possible RBD had slightly less education (estimated mean, 13.2 years vs. 13.6 years) and lower income, compared with controls. Participants with possible RBD retired at a slightly younger age (57.5 years vs. 58.6 years) and were more likely to have retired because of health concerns (28.9% vs. 22.0%), compared with controls.

In addition, patients with possible RBD were more likely to drink more and to be moderate to heavy drinkers than controls; they were also more likely to be current or past smokers. Antidepressant use was more frequent and psychological distress was greater among participants with possible RBD.

When the investigators performed a multivariable logistic regression analysis, the associations between possible RBD and male sex and relationship status remained. Lower educational level, but not income level, also remained associated with possible RBD. Furthermore, retirement age and having reported retirement because of health concerns remained significantly associated with possible RBD, as did the amount of alcohol consumed weekly and moderate to heavy drinking. Sensitivity analyses did not change the results significantly.

One of the study's limitations is its reliance on self-report to identify participants with possible RBD, the authors wrote. The prevalence of possible RBD in the study was 3.2%, but research using polysomnography has found a prevalence of about 1%. Thus, the majority of cases in this study may have other disorders such as restless legs syndrome or periodic limb movements. Furthermore, many participants who enact their dreams (such as unmarried people) are likely unaware of it. Finally, the researchers did not measure several variables of interest, such as consumption of caffeinated products.

"The main advantages of our current study are the large sample size; the systematic population-based sampling; the capacity to adjust for diverse potential confounding variables, including mental illness; and the ability to screen out RBD mimics," the authors concluded. **NR**

—Erik Greb

Suggested Reading

Yao C, Fereshtehnejad S, Keezer MR, et al. Risk factors for possible REM sleep behavior disorder: a CLSA population-based cohort study. *Neurology*. 2018 Dec 26 [Epub ahead of print].

NEWSROUNDUP

Are hospitalizations associated with cognitive decline?

Nonelective hospitalizations are associated with faster cognitive decline in older adults, according to research published online Jan. 11 in *Neurology*. Researchers analyzed data from the Rush Memory and Aging Project, a prospective study of older adults without baseline dementia. The investigators linked annual measures of cognition to Medicare claims records. Of 777 participants, 59.2% were hospitalized over a mean of 5 years; 28.6% had at least one elective hospitalization, and 53.8% had at least one nonelective hospitalization. Mixed-effects regression models, adjusted for age, sex, education, medical conditions, length of stay, surgery, intensive care unit, and comorbidities, found that patients who were not hospitalized had a mean loss of 0.051 units of global cognition per year. The rate of loss before or after elective hospitalizations was not significantly different. In contrast, decline before nonelective hospitalizations was faster—0.076 units per year—and accelerated to a mean loss of 0.112 units per year after nonelective hospitalizations.

Physical activity in old age may protect cognition

Older adults who move more through daily exercise or routine activities like housework may preserve more of their cognition, according to a study published online Jan. 16 in *Neurology*. To examine the associations of physical activity, cognition, and brain pathologies (e.g., Alzheimer's disease), researchers studied 454 brain autopsies from decedents in a clinical–pathologic cohort study who had completed cognitive tests and worn accelerometers to measure physical activity. The investigators conducted regression analyses to assess associations of physical activity and brain pathologies with global cognition proximate to death, controlling for age, sex, education, and motor abilities. Higher levels of total daily activity and better motor abilities were independently associated with better cognition. These associations remained significant when researchers accounted for brain pathologies, as well as in sensitivity analyses that excluded cases with poor cognition or dementia.

How seizure prediction may benefit patients with epilepsy

Stress levels, EEG readings, and circadian patterns someday may be used to generate a daily seizure forecast, a researcher suggests.

NEW ORLEANS—For people with epilepsy, "the sudden and apparently unpredictable nature of seizures is one of the most disabling aspects of having the disorder," said Michael Privitera, MD. Reliable seizure forecasts could help patients stay safe, improve their quality of life, and create intervention opportunities to prevent seizures.

If a patient knew that "tomorrow will be a dangerous day" with a 50% chance of having a seizure, the patient could avoid hazardous activities, try to reduce stress, or increase supervision to reduce the risk of sudden, unexpected death in epilepsy, said Dr. Privitera, professor of neurology and director of the epilepsy center at the University of Cincinnati Gardner Neuroscience Institute. Physicians might be able to intervene during high-risk periods by altering antiepileptic drug regimens.

Evidence suggests that seizure prediction is possible today and that advances in wearable devices and analysis of chronic EEG recordings likely will improve the ability to predict seizures, Dr. Privitera said at the annual meeting of the American Epilepsy Society. Studies have found that some patients can predict the likelihood of seizures in the next 24 hours better than chance. In the future, algorithms that incorporate variables such as pulse, stress, mood, electrodermal activity, circadian rhythms, and EEG may further refine seizure prediction.

A complex picture

One problem with predicting seizures is that "you can have substantial changes in the seizure tendency, but not have a seizure," Dr. Privitera said. Stress, alcohol, and missed medications, for example, may affect the seizure threshold. "They may be additive, and it may be when those things all hit at once that a seizure happens."

Many patients report prodromal or premonitory symptoms before a seizure. "Most of us as clinicians will say, 'Well, maybe you have some inkling, but I don't think you're really able to predict it,'" Dr. Privitera said.

Sheryl R. Haut, MD, professor of neurology at the Albert Einstein College of Medicine, New York, and her colleagues prospectively looked at patient self-prediction in 2007. The investigators followed 74 people with epilepsy who completed a daily diary in which they predicted the likelihood of a seizure occurring in the next 24 hours. Their analysis included approximately 15,000 diary days and 1,400 seizure days.

A subset of participants, about 20%, was significantly better than chance at predicting when a seizure would happen. If a patient in this subgroup said that a seizure was extremely likely, then a seizure occurred approximately 37% of the time. If a patient predicted that a seizure was extremely unlikely, there was about a 10% chance of having a seizure.

"This was a pretty substantial difference," Dr. Privitera said. Combining patients' predictions with their self-reported stress levels seemed to yield the most accurate predictions.

Stress and the SMILE study

About 90% of people with epilepsy identify at least one seizure precipitant, and the most commonly cited trigger is stress. When Dr. Privitera and his colleagues surveyed patients in their clinic, 82% identified stress as a trigger. More than half of these patients had used some form of stress reduction, such as exercise, yoga, or meditation; 88% of those patients thought that stress reduction helped their seizures.

Underlying anxiety was the only difference between patients who thought that their seizures were triggered by stress and those who did not. Patients who did not think that stress triggered their seizures had significantly lower scores on the Generalized Anxiety Disorders–7.

Subsequently, Dr. Haut, Dr. Privitera, and colleagues conducted the Stress Management Intervention for Living with Epilepsy (SMILE) study, a prospective, controlled trial assessing the efficacy of a stress reduction intervention for reducing seizures, as well as measuring seizure self-prediction. The researchers randomized patients to a progressive muscle relaxation intervention or to a control group; patients in the control group wrote down their activities for the day.

Michael Privitera, MD

Patients posted diary entries twice daily into a smartphone, reporting stress levels and mood-related variables. As in Dr. Haut's earlier study, patients predicted whether having a seizure was extremely unlikely, unlikely, neutral, likely, or extremely likely. Mood and stress variables (such as feeling unpleasant or pleasant, relaxed or stressed, and not worried or extremely worried) were ranked on a visual analog scale from 0 to 100.

The trial included participants who had at least two seizures per month and any seizure trigger. Medications were kept stable throughout the study. During a 2-month baseline, patients tracked their seizures and stress levels. During the 3-month treatment period, patients received the active or control intervention.

In all, 64 subjects finished the study, completing all diary entries on 94% of the days. In the active-treatment group, median seizure frequency decreased by 29%, compared with a 25% decrease in the control group. However, the difference between the groups was not statistically significant. Although the 25% reduction in the control group probably is partly attributable to the placebo effect, part of the decrease may be related to a mindfulness effect from completing the diary, Dr. Privitera said.

The active-treatment group had a statistically significant reduction in self-reported stress, compared with the control group, but this decrease did not correlate with seizure reduction. Changes in anxiety levels also did not correlate with seizures.

"It does not disprove the [stress] hypothesis, but it does tell us that there is more going on with stress and seizure triggers than just patients' self-reported stress," Dr. Privitera said.

Patients' predictions

The seizure prediction findings in SMILE were similar to those of Dr. Haut's earlier study. Among the 10 best predictors out of the 64 participants, "when they said that a seizure was extremely likely, they were 8.36 times more likely to have a seizure than when they said a seizure was extremely unlikely," Dr. Privitera said.

Many patients seemed to increase their predicted seizure probabilities in the days after having a seizure. In addition, feeling sad, nervous, worried, tense, or stressed significantly increased the likelihood that a patient would predict that a seizure was coming. However, these feelings were "not very accurate [for predicting] seizures," he said. "Some people are better predictors, but really the basis of that prediction remains to be seen. One of my hypotheses is that some of these people may be responding to subclinical EEG changes."

Together, these self-prediction studies include data from 4,500 seizures and 26,000 diary entries and show that "there is information in patient self-report that can help us in understanding how to predict and when to predict seizures," Dr. Privitera said.

Multivariable models may improve seizure prediction

Incorporating cardiac, EEG, and other variables

Various other factors may warrant inclusion in a seizure forecasting system. A new vagus nerve stimulation system responds to heart rate changes that occur at seizure onset. And for decades, researchers have studied the potential for EEG readings to predict seizures. A 2008 analysis of 47 reports concluded that limited progress had been made in predicting a seizure from interictal EEG. Now, however, long-term intracranial recordings are providing new and important information about EEG patterns.

Whereas early studies examined EEG recordings from epilepsy monitoring units—when patients may have been sleep deprived, had medications removed, or recently undergone surgery—chronic intracranial recordings from devices such as the RNS (responsive neurostimulation system) have allowed researchers to look long term at EEG changes that are more representative of patients' typical EEG patterns.

The RNS detects interictal spikes and seizure discharges and provides an electrical stimulation to stop seizures. "When you look at these recordings, there are a lot more electrographic seizures than clinical seizures that trigger these stimulations," said Dr. Privitera. "If you look at somebody with a typical RNS, they may have 100 stimulations in a day and no clinical seizures. There are lots and lots of subclinical electrographic bursts—and not just spikes, but things that look like short electrographic seizures—that occur throughout the day."

A handheld device

Researchers in Melbourne designed a system that uses implanted electrodes to provide chronic recordings. An algorithm then learned to predict the likelihood of a seizure from the patient's data as the system recorded over time. The system could indicate when a seizure was likely by displaying a light on a handheld device. Patients were recorded for between 6 months and 3 years.

"There was a statistically significant ability to predict when seizures were happening," Dr. Privitera said. "There is information in long-term intracranial recordings in many of these people that will help allow us to do a better prediction than what we are able to do right now, which is essentially not much."

This research suggests that pooling data across patients may not be an effective seizure prediction strategy because different epilepsy types have different patterns. In addition, an individual's patterns may differ from a group's patterns. Complicating matters, individual patients may have multiple seizure types with different onset mechanisms.

"Another important lesson is that false positives in a deterministic sense may not represent false positives in a probabilistic sense," Dr. Privitera said. "That is, when the seizure prediction program, whether it is the diary or the intracranial EEG or anything else, says the threshold changed, but you did not have a seizure, it does not mean that your prediction system was wrong. If the seizure tendency is going up … and your system says the seizure tendency went up, but all you are measuring is actual seizures, it looks like it is a false-positive prediction of seizures. But in fact it is a true-positive prediction of the seizure tendency changing but not necessarily reaching seizure threshold."

Multiday patterns

Recent research shows that "we are just at the start," Dr. Privitera said. "There are patterns underlying seizure frequency that … we are only beginning to be able to look at because of these chronic recordings."

Baud et al. analyzed interictal epileptiform activity and seizures in patients who have had responsive neurostimulators for as long as 10 years. "What they found was that interictal spikes and rhythmic discharges oscillate with circadian and multiday periods that differ from person to person," Dr. Privitera said. "There were multiday periodicities, most commonly in the 20- to 30-day duration, that were relatively stable over periods of time that lasted up to years."

Researchers knew that seizures in women of childbearing age can cluster in association with the menstrual cycle, but similar cycles also were seen in men. In addition, the researchers found that seizures "occur preferentially during the rising phase of these multiday interictal rhythms," which has implications for seizure forecasts, Dr. Privitera noted.

Stress biomarkers and wearables

Future seizure prediction methods may incorporate other biomarkers, such as stress hormones. A researcher at the University of Cincinnati, Jason Heikenfeld, PhD, is conducting research with a sensor that sticks to the wrist and measures sweat content, Dr. Privitera said. The technology originally was developed to measure sodium and potassium in sweat, but Dr. Privitera's group has been working with him to measure cortisol, which may be a biomarker for stress and be useful for seizure prediction.

"Multivariate models are needed. We have lots of different ways that we can look at seizure prediction, and most likely the most accurate seizure prediction programs will incorporate multiple different areas," Dr. Privitera said. "Seizure forecasting is possible. We can do it now. We can probably do it better than chance in many patients. … It is important because changes in seizure likelihood could lead to pharmacologic or device or behavioral interventions that may help prevent seizures."

Dr. Privitera reported conducting contracted research for Greenwich and SK Life Science and receiving consulting fees from Upsher-Smith and Astellas. **NR**

—Jake Remaly

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Cook MJ, O'Brien TJ, Berkovic SF, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. *Lancet Neurol.* 2013;12(6):563-571.

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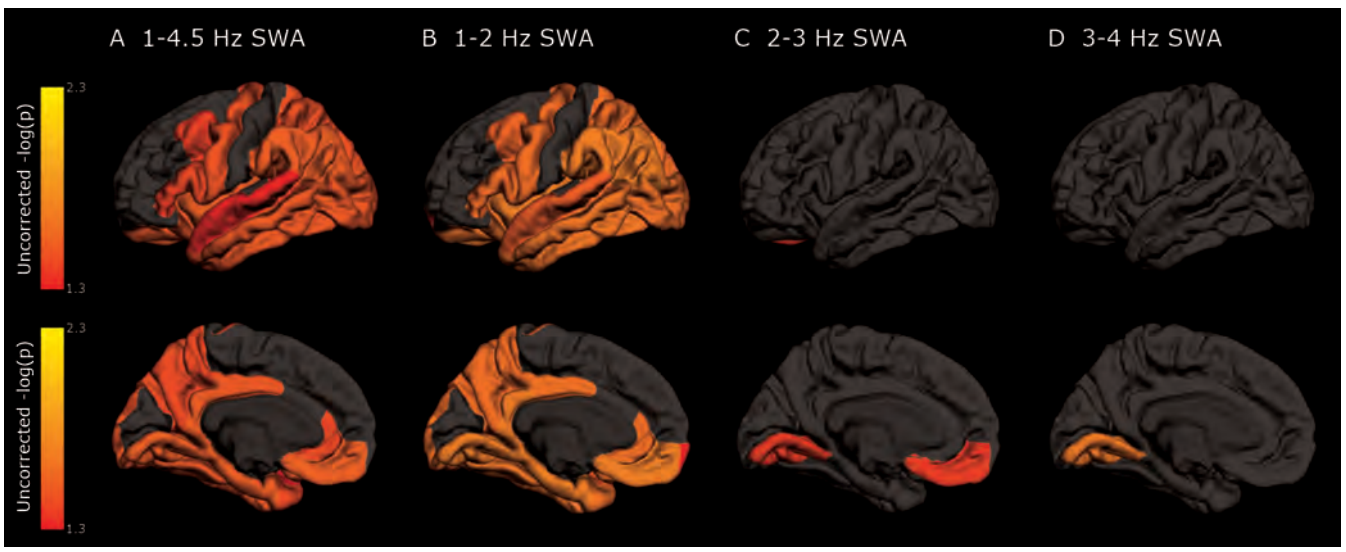
Non-REM sleep is inversely related to Alzheimer's disease pathology

EEG and brain imaging indicate an association between disrupted sleep patterns and tau and amyloid deposition.

Decreased time in deep, dreamless sleep is associated with increasing Alzheimer's disease pathology, particularly tau deposition, in cognitively normal subjects.

The protein was evident in areas associated with memory consolidation that typically are affected in Alzheimer's disease, including the entorhinal, parahippocampal, inferior parietal, insula, isthmus cingulate, lingual, supramarginal, and orbitofrontal regions.

Because the findings were observed in a population of cognitively normal and minimally impaired subjects, they suggest a role for sleep studies in assessing the risk for cognitive decline and Alzheimer's disease and in monitoring patients with the disease, reported Brendan P. Lucey, MD, and his colleagues. Their study appeared in *Science Translational Medicine*.



PET imaging shows a correlation between accumulation of tau in the brain (orange regions) and lower levels of non-REM slow wave activity (SWA). The association is driven by the lowest SWA frequency range of 1-2 Hz.

CREDIT: Lucey BP, et al. *Science Translational Medicine.* (2018).

Subjects participated in longitudinal aging studies

"With the rising incidence of Alzheimer's disease in an aging population, our findings have potential application in both clinical trials and patient screening for Alzheimer's disease to noninvasively monitor for progression of Alzheimer's disease pathology," wrote Dr. Lucey, director of the Sleep Medicine Center and assistant professor of neurology at Washington University in St. Louis. "For instance, periodically measuring non-REM slow wave activity, in conjunction with other biomarkers, may have utility for monitoring Alzheimer's disease risk or response to an Alzheimer's disease treatment."

Dr. Lucey and his colleagues examined sleep architecture and tau and amyloid deposition in 119 subjects enrolled in longitudinal aging studies. For 6 nights, subjects slept while wearing a single-channel EEG monitor. They also underwent cognitive testing and genotyping for Alzheimer's disease risk factors.

Subjects were a mean of 74 years old. Almost 80% had normal cognition, as measured by the Clinical Dementia Rating Scale (CDR); the remainder had very mild cognitive impairment (CDR, 0.5).

Pathology affected many sleep variables

Among those with positive biomarker findings, sleep architecture was altered in several ways. These patients had lower REM latency, lower wake after sleep onset, prolonged sleep-onset latency, and longer self-reported total sleep time. The differences were evident in those with normal cognition, but more pronounced in those with mild cognitive impairment. Despite the longer sleep times, however, sleep efficiency was decreased.

Decreased non-REM slow wave activity was associated with increased tau deposition. The protein was largely concentrated in areas typically affected in Alzheimer's disease pathology (i.e., entorhinal, parahippocampal, orbitofrontal, precuneus, inferior parietal, and inferior temporal regions). There were no significant associations between non-REM slow wave activity and amyloid deposits.

Other sleep parameters, however, were associated with amyloid deposition, including REM latency and sleep latency, "suggesting that as amyloid-beta deposition increased, the time to fall asleep and enter REM sleep decreased," the investigators said.

Those with tau pathology also slept longer, reporting more daytime naps. "This suggests that participants with greater tau pathology experienced daytime sleepiness despite increased total sleep time.

"These results, coupled with the non-REM slow wave activity findings, suggest that the quality of sleep decreases with increasing tau despite increased sleep time," said the authors. Questions about napping should probably be included in dementia screening discussions, they added.

The study was largely funded by the National Institutes of Health. Dr. Lucey had no financial conflicts. **NR**

—Michele G. Sullivan

Suggested Reading

Lucey BP, McCullough A, Landsness EC, et al. Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease. *Sci Transl Med.* 2019 Jan 9 [Epub ahead of print].

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Cerebral small vessel disease progression linked to MCI in hypertensive patients

Periventricular white matter hyperintensities in patients with hypertension were associated with sixfold higher odds of mild cognitive impairment.

Patients with hypertension who show substantial progression of cerebral small vessel disease over time have sixfold higher odds of developing mild cognitive impairment (MCI) than do those without signs of progression on brain MRI, new research has found.

The results, published online January 4 in *Hypertension*, come from a longitudinal, population-based study of 976 patients with hypertension but with no history of dementia or clinical stroke. Participants underwent a vascular risk assessment, brain MRI, cognitive evaluation, and blood sampling at baseline, and 345 patients were retested after a mean of nearly 4 years.

Researchers saw significant sixfold higher odds of developing incident MCI among individuals who showed marked progression of periventricular white matter hyperintensities—an imaging hallmark of cerebral small vessel disease—compared with individuals who did not show any progression (odds ratio, 6.184; 95% confidence interval, 1.506-25.370; $P = .011$).

Patients with greater progression of periventricular white matter hyperintensities also showed significantly greater decreases in global cognition scores—in total Dementia Rating Scale (DRS-2) z-score and executive function z-score—when compared against individuals without white matter hyperintensity progression.

"As MCI is one of the most important risk factors in the development of dementia, future research should investigate the mechanisms by which periventricular white matter hyperintensities trigger cognitive impairment and the clinical utility of its assessment," wrote Joan Jiménez-Balado of Vall d'Hebron Research Institute, Barcelona, and his associates.

However, deep white matter hyperintensity progression—as opposed to periventricular—was not linked to cognitive changes, except in the case of bilateral occipital deep white matter hyperintensity changes, which were linked to a significant worsening in the attention z-score.

Network disruptions?

The authors noted that the different impacts of periventricular versus deep white matter hyperintensities may relate to a number of factors. The first was that deep white matter hyperintensities disrupt corticocortical connections but periventricular ones are more likely to affect long cortico–subcortical association fibers, which "would be an important variable to determine the impaired networks involved in cognition."

They also suggested that periventricular and deep white matter hyperintensities may affect different neuromodulator systems; the periventricular white matter could be closer to ascending cholinergic bundles that may play a role in vascular cognitive impairment.

Periventricular white matter hyperintensities may also accelerate the deposition of amyloid because of their association with venous collagenosis, which is linked to ischemia and disruptions of the interstitial fluid circulation.

"On the other hand, [deep white matter hyperintensity] may be more related to hypoperfusion, as deep areas are particularly vulnerable to low [blood pressure]," the authors wrote, while stressing that the pathophysiology of white matter hyperintensities is not fully understood, so further research is needed.

Overall, the 345 patients with follow-up data had a median age of 65 years at baseline and mean blood pressure of 143/78.2 mm Hg at baseline and 146.5/75 mm Hg at follow-up. White matter hyperintensity changes occurred periventricularly in 22% and in deep white matter in 48%. The researchers saw new infarcts in 6.1% of patients, and 5.5% had incident cerebral microbleeds. While incident cerebral microbleeds were significantly associated with declines in the attention z-score, they did not affect other cognitive functions, and incidental infarcts were also not associated with cognitive changes.

Correlations with diastolic blood pressure

Baseline blood pressure and average blood pressure during follow-up were not associated with changes in cardiac small vessel disease lesions. However, diastolic—but not systolic—blood pressure at baseline and follow-up was positively correlated with total, attention, and executive function DRS-2 z-scores at follow-up.

Three-quarters of patients showed cognitive changes associated with normal aging at baseline and follow-up, 9.1% had stable MCI, and 9.1% of patients had incident MCI. However, 6.6% of subjects reverted to normal aging after having MCI at baseline.

The authors noted that they did not examine markers of neurodegeneration, such as tau or amyloid-beta, which could also be linked to hypertension and cerebral small vessel disease lesions.

The study was supported by Instituto de Salud Carlos III, AGAUR (Agency for Management of University and Research Grants), the Secretary of Universities and Research of the Department of Economy and Knowledge, and the European Regional Development Fund. The authors said they have no conflicts of interest. **NR**

—Bianca Nogrady

Suggested Reading

Jiménez-Balado J, Riba-Llena I, Abril O, et al. Cognitive impact of cerebral small vessel dsease changes in patients with hypertension. *Hypertension.* 2019;73(2):342-349.

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Integrated analysis suggests cladribine's safety in MS

Cladribine is not associated with an increased risk of infections or malignancy, and treatment-induced lymphopenia is transient.

Cladribine tablets (3.5 mg/kg) have a favorable adverse event profile and are safe as monotherapy for relapsing-remitting multiple sclerosis (MS), according to an integrated analysis of several clinical trials published online ahead of print in *Multiple Sclerosis and Related Disorders*.

The drug causes transient lymphopenia, as is to be expected from its mechanism of action, but most patients who receive cladribine do not have grade 3 or 4 lymphopenia, the study authors wrote. In general, they said, cladribine is not associated with an increased risk of infections or malignancy.

Data indicate that cladribine's mechanism of action contributes to its durable clinical effect, despite the brief treatment periods. Clinical trials have provided information about the treatment's safety and tolerability. To examine the treatment's long-term safety, Stuart Cook, MD, of Rutgers, the State University of New Jersey, Newark, and his colleagues pooled data for patients with MS treated with cladribine tablets (3.5 mg/kg) as monotherapy or placebo in three phase 3 clinical trials (CLARITY, CLARITY Extension, and ORACLE-MS) and followed up in the PREMIERE registry. The investigators called these patients the monotherapy oral cohort.

To investigate the potential associations between cladribine and rarer adverse events such as malignancies, Dr. Cook and his colleagues examined data from patients with MS who received cladribine, regardless of the formulation or route of administration, or placebo (the all-exposed cohort). This cohort included data from the ONWARD trial, in which patients received cladribine tablets or placebo in combination with interferon-beta, as well as data from five trials in which patients received parenteral cladribine or placebo.

The monotherapy oral cohort included 923 patients who received cladribine and 641 who received placebo. The median age at enrollment in this cohort was approximately 36 years. The majority of patients were women and disease characteristics were balanced between arms. The all-exposed cohort included 1,926 patients who received cladribine and 802 who received placebo. The demographic characteristics of this cohort were similar to those of the monotherapy oral cohort.

In the monotherapy oral cohort, the incidence rate of treatment-emergent adverse events, in adjusted adverse events per 100 patient-years, was 103.29 for the active group versus 94.26 for controls. Lymphopenia (7.94 vs. 1.06) and decreased lymphocyte count (0.78 vs. 0.10) occurred more frequently in the active group than in the placebo group.

Herpes zoster also occurred more frequently in the cladribine group (0.83 vs. 0.20). However, cladribine was not associated with systemic serious disseminated herpes zoster. Furthermore, the investigators found no overall increased risk of infections, including opportunistic infections, with cladribine tablets versus placebo, except for herpes zoster.

In addition, Dr. Cook and his colleagues found no increase in malignancy rates among patients who received cladribine, compared with those who received placebo. They also found no increase in the incidence of malignancies over time in the cladribine group.

The adverse event profile for cladribine tablets (3.5 mg/kg) as monotherapy has been well characterized, the investigators wrote. The results of this analysis are broadly similar to the short-term adverse event results reported in the individual trials.

EMD Serono and Merck Serono, two affiliates of Merck in Darmstadt, Germany, sponsored the study. Merck manufactures cladribine. **NR**

—Erik Greb

Suggested Reading

Cook S, Leist T, Comi G, et al. Safety of cladribine tablets in the treatment of patients with multiple sclerosis: an integrated analysis. *Mult Scler Relat Disord.* 2018 Nov 18 [Epub ahead of print].

FDA reaffirms its rules for cannabis compounds

A new federal law legalizes hemp production, but the FDA will continue to regulate all cannabis and cannabis-derived products.

The newly enacted Agriculture Improvement Act of 2018 legalizes hemp production and use, but the Food and Drug Administration's regulation of cannabis and cannabis-derived products remains unchanged. The act (H.R. 2) revamps federal authorities' regulatory approach to hemp production. The law removes hemp from the Controlled Substances Act, which means it is no longer an illegal substance. Hemp is now defined as cannabis and derivatives of cannabis that have extremely low concentrations (less than 0.3%, on a dry weight basis) of the psychoactive compound delta-9-tetrahydrocannabinol (THC).

Despite hemp's new legal status, FDA Commissioner Scott Gottlieb, MD, said the FDA's regulation of cannabis and cannabis-derived products remains the same. "In short, we treat products containing cannabis or cannabis-derived compounds as we do any other FDA-regulated products," Dr. Gottlieb said in a Dec. 20, 2018, statement published on the FDA website. That means "they are subject to the same authorities and requirements as FDA-regulated products containing any other substance."

The regulation of those products will be the same regardless of the source of the substance, including plants classified as hemp. The FDA will require cannabis and cannabis-derived products to undergo testing similar to that for other drug products, given the concern regarding medical claims made about those products.

"Cannabis and cannabis-derived products claiming in their marketing and promotional materials that they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases (such as cancer, Alzheimer's disease, psychiatric disorders, and diabetes) are considered new drugs or new animal drugs," Dr. Gottlieb explained. And they "must go through the FDA drug approval process for human or animal use before they are marketed in the United States."

Selling unapproved products with unsubstantiated claims is a "violation of the law," he said. In addition, "it is unlawful under the [Food, Drug, & Cosmetics Act] to introduce food containing added CBD [cannabidiol] or THC into interstate commerce, or to market CBD or THC products as, or in, dietary supplements, regardless of whether the substances are hemp-derived," Dr. Gottlieb noted. That is because CBD and THC are active ingredients in FDA-approved drugs.

Commissioner Gottlieb also noted that "pathways remain available for the FDA to consider whether there are circumstances in which certain cannabis-derived compounds might be permitted in a food or dietary supplement." The FDA announced plans for a future meeting to discuss the lawful marketing of hemp-derived foods that do not contain CBD or THC. **NR**

—Gregory Twachtman

Prenatal valproate exposure raises ADHD risk

Children whose mothers used valproate between 30 days before conception and birth had a 48% increased risk of ADHD, compared with children whose mothers did not use valproate.

Children exposed to valproate in utero were 48% more likely to be diagnosed with ADHD when compared with unexposed children in a population-based cohort study of more than 900,000 children in Denmark.

Antiepileptic drug exposure is associated with an increased risk of various congenital malformations, but its role in the development of ADHD in children has not been well documented, first author Jakob Christensen, MD, PhD, DrMedSci, of Aarhus (Denmark) University Hospital, and his colleagues wrote in their paper, published online Jan. 4 in *JAMA Network Open*.

The researchers identified 913,302 singleton births in Denmark from 1997 through 2011. Children were followed through 2015.

> Data from the current study differ from a meta-analysis of five studies that did not find an increase in ADHD risk.

Increase seen in observational study

Overall, children who were prenatally exposed to valproate had a 48% increased risk of ADHD. Antiepileptic drug exposure was defined as 30 days before the estimated day of conception to the day of birth, and included valproate, clobazam, and other antiepileptic drugs. The average age of the children at the study's end was 10 years, and approximately half were male.

A total of 580 children were exposed to valproate in utero; of these, 8.4% were later diagnosed with ADHD, compared with 3.2% of 912,722 children who were not exposed to valproate. In addition, the absolute 15-year risk of ADHD was 11% in valproate-exposed children vs. 4.6% in unexposed children. No significant associations appeared between ADHD and other antiepileptic drugs.

The study was limited by several factors, including the contraindication of valproate for use in pregnancy, which may mean that the women taking valproate had more severe disease, the researchers noted.

"Due to the observational nature of this study, we cannot rule out that the observed risk increase for ADHD is at least in part explained by the mother's health condition that triggered the prescription of valproate during pregnancy," they said. Other limitations included a lack of data on the exact amounts of valproate taken during pregnancy and the potential impact of nonepilepsy medications, they noted.

However, the results were strengthened by the large size and population-based cohort and support warnings by professional medical organizations against valproate use in pregnancy, the researchers said. "As randomized clinical trials of valproate use during pregnancy are neither feasible nor ethical, our study provides clinical information on the risk of ADHD associated with valproate use during pregnancy," they concluded.

Counsel patients, continue research

The data from the current study differ from those of a recent meta-analysis of five studies that did not find a statistically significant increase in ADHD risk in children associated with prenatal valproate exposure, Kimford J. Meador, MD, wrote in an accompanying editorial.

"The discrepancy between the present study and the prior meta-analysis might be due to the meta-analysis using different analytical approaches and examining studies with smaller sample sizes, higher attrition rates, shorter follow-ups, and cohort differences," Dr. Meador said. "Nevertheless, the findings by Christensen et al. are consistent with multiple studies demonstrating adverse neurodevelopmental effects associated with fetal valproate exposure."

Given the potential risks associated with valproate exposure not only for behavior problems such as ADHD, but also for congenital malformations and other cognitive and behavioral issues in children, women of childbearing age who are using valproate or considering a prescription should be counseled for informed consent, Dr. Meador said.

Dr. Meador advocated additional research on the impact of antiepileptic drugs during pregnancy and risk assessment strategies, including "a national reporting system for congenital malformations, routine preclinical testing of all new antiseizure medications for neurodevelopmental effects, monitoring of antiseizure medication prescription practices for women of childbearing age to determine whether emerging knowledge is being appropriately applied, and improved funding of basic and clinical research to fully delineate risks and underlying mechanisms of anatomical and behavioral teratogenesis from antiseizure medications."

The study was supported by grants to various authors from the Danish Epilepsy Association Central Denmark Region, the Aarhus University Research Foundation, the Lundbeck Foundation, the National Institutes of Health, the Novo Nordisk Foundation, and the European Commission.

Dr. Meador is affiliated with the department of neurology and neurological sciences at Stanford (Calif.) University. He disclosed research support from the National Institutes of Health and Sunovion, and travel support from UCB. The Epilepsy Study Consortium pays Stanford University for his research consultant time related to Eisai, GW Pharmaceuticals, NeuroPace, Novartis, Supernus, UCB, Upsher-Smith Laboratories, and Vivus. **NR**

—*Heidi Splete*

Suggested Reading

Christensen J, Pedersen LH, Sun Y, et al. Association of prenatal exposure to valproate and other antiepileptic drugs with risk for attention-deficit/hyperactivity disorder in offspring. *JAMA Netw Open.* 2019;2(1):e186606.

Meador KJ. Fetal valproate exposure and attention-deficit/hyperactivity disorder. *JAMA Netw Open.* 2019;2(1):e186603.

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Gene therapy for Parkinson's disease fosters a new brain circuit

New polysynaptic functional pathways may be the mechanism by which gene therapy produces therapeutic effects.

A gene therapy for Parkinson's disease that focuses on the subthalamic nucleus appears to lead to the formation of unique brain circuitry that correlates with clinical improvement.

In a paper published online Nov. 28, 2018, in *Science Translational Medicine,* researchers described the findings of a metabolic imaging study that explored the mechanism underlying benefits seen in a phase 2, blinded, sham-controlled clinical trial of the gene therapy. The therapy used an adeno-associated viral vector to deliver the gene for glutamic acid decarboxylase into the subthalamic nucleus, which is overactivated in Parkinson's disease. The gene was intended to inhibit the neurons in that region.

Martin Niethammer, MD, PhD, of the Center for Neurosciences at the Feinstein Institute for Medical Research in New York, and his coauthors used ^{18}F-fluorodeoxyglucose PET at baseline, 6 months, and 12 months in 15 gene-therapy patients and 21 sham-treated patients. This imaging revealed the development of a new brain circuit in patients treated with the gene therapy.

The circuit, which researchers called the glutamic acid decarboxylase-related pattern (GADRP), was distinguished by increased metabolism in the premotor region that extended into the adjacent motor cortex and the supramarginal gyrus. The pattern also encompassed decreased metabolic activity in the caudate, anterior putamen, and adjacent globus pallidus; the ventral anterior and medial dorsal thalamic nuclei; and the inferior frontal gyrus.

All 15 patients who received the gene therapy showed a significant trend in GADRP expression after the treatment, compared with patients who underwent the sham procedure. Furthermore, these trends correlated significantly with improved clinical outcomes.

The imaging also revealed increased new connections between regions in the GADRP space among patients who received the gene therapy. Researchers noted five new intrahemispheric node-to-node connections in these patients that were not seen in the sham procedure group. These connections included one linking the left caudate nucleus to the left superior frontal node, one linking the right superior frontal node to the right supramarginal gyrus, and one linking the left anterior putamen and globus pallidus to the ipsilateral thalamic node. The authors also found that overall connectivity in the network rose to abnormal levels 12 months after gene therapy, while no similar increases were seen in the sham group.

Given that deep brain stimulation (DBS) for Parkinson's disease also targets the subthalamic nucleus, researchers looked at changes to the GADRP network in patients receiving DBS, compared with those who received sham therapy and those who received gene therapy. They saw that changes in GADRP expression were significantly different between the gene therapy-treated patients and those treated with DBS and sham surgery. However, the differences between DBS and sham surgery were not significant.

"The current study indicates that customized networks can be characterized using functional imaging data ... and, if validated, could be used as quantitative outcome measures in more definitive, later-stage clinical trials," the authors wrote.

The study was supported by Neurologix. Two authors were consultants and stockholders of MeiraGTx. **NR**

—Bianca Nogrady

Suggested Reading

Niethammer M, Tang CC, Vo A, et al. Gene therapy reduces Parkinson's disease symptoms by reorganizing functional brain connectivity. *Sci Transl Med.* 2018 Nov 28 [Epub ahead of print].

How often is AED treatment delayed for patients with epilepsy?

More than 30% of patients with newly diagnosed epilepsy do not initiate antiepileptic drug treatment at the time of diagnosis, according to an Australian study.

NEW ORLEANS—More than 30% of patients with newly diagnosed epilepsy do not initiate antiepileptic drug (AED) treatment at the time of diagnosis, according to an Australian study presented at the annual meeting of the American Epilepsy Society. Most untreated patients begin an AED after experiencing subsequent seizures, however.

"The decision to start or withhold treatment reflects the complex interplay between factors perceived to influence the predicted risk of seizure recurrence, which remain imprecise, and personal factors," said lead study author Zhibin Chen, PhD, a biostatistician at the University of Melbourne, and colleagues.

Many patients with epilepsy in resource-poor countries may not receive AED therapy for socioeconomic reasons, but little is known about untreated epilepsy in high-income countries. To assess the extent of and reasons for patients not receiving AEDs when treatment is accessible and affordable, Dr. Chen and colleagues prospectively recruited adult patients who attended the first-seizure clinics of publicly funded hospitals in Western Australia between May 1, 1999, and May 31, 2016. The patients had new-onset seizures and were referred by primary care or emergency department physicians. The health care system provided universal coverage for patients' hospital admissions, outpatient visits, investigations, and treatment.

The researchers identified patients with newly diagnosed epilepsy and reviewed medical records to determine the proportion of untreated patients and the reasons for not starting treatment at each follow-up visit. The investigators compared the sociodemographic factors, neuroimaging, and EEG findings of treated and untreated patients.

In all, 1,317 people attended the clinics during the study period, and 610 patients (61% male; median age, 40) received a diagnosis of epilepsy and met 2014 International League Against Epilepsy (ILAE) diagnostic criteria for epilepsy. Patients were followed for a median of 5.7 years.

Of the 610 patients with epilepsy, 31% did not start AED treatment at the time of diagnosis, 16.4% because the neurologist did not recommend treatment and 14.6% because the patient declined treatment despite a neurologist's recommendation to start therapy.

Patients' reasons for not starting treatment included doubts about the need for treatment or about the epilepsy diagnosis, as well as concerns about medication side effects. Neurologists' reasons for not beginning treatment included a patient having only one seizure and awaiting further results. The presence of seizure-precipitating factors (e.g., flashing lights, sleep deprivation, stress, or alcohol use) was another reason that patients and neurologists commonly cited for not initiating treatment.

Among the 189 initially untreated patients, 62.4% started treatment after a median delay of 95 days, "mainly after further seizures," the investigators said. Patients with epilepsy who were older, from lower socioeconomic areas, had experienced more seizures, or had epileptogenic lesions on neuroimaging were more likely to initiate AED treatment at diagnosis.

This study was supported by a grant from UCB Pharma. **NR**

—Jake Remaly

Does rituximab delay disability progression in patients with secondary progressive MS?

Patients treated with rituximab off label may accrue less disability during follow-up, compared with matched controls.

Patients with secondary progressive multiple sclerosis (MS) who are treated with rituximab have significantly lower Expanded Disability Status Scale (EDSS) scores during follow-up and significantly delayed confirmed disability progression, compared with matched controls, according to a retrospective analysis published online January 7 in *JAMA Neurology*.

The results suggest that "B-cell depletion by rituximab may be therapeutically beneficial in these patients," said lead author Yvonne Naegelin, MD, of University Hospital Basel, Switzerland, and her colleagues.

Research indicates that B cells play a role in the pathogenesis of relapsing-remitting and secondary progressive MS, and rituximab, a monoclonal CD20 antibody, may deplete B cells in the peripheral immune system and CNS.

The researchers compared disability progression in patients treated with rituximab at MS centers in Switzerland with disability of control patients with secondary progressive MS who did not receive rituximab. Data for the present analysis were collected between 2004 and 2017.

The investigators matched rituximab-treated and control patients 1:1. Variables were sex, age, EDSS score, and disease duration at baseline. Rituximab-treated patients had a mean age of 49.7 years, mean disease duration of 18.2 years, and mean EDSS score of 5.9; 59% were women. Controls had a mean age of 51.3 years, mean disease duration of 19.4 years, and mean EDSS score of 5.7; 61% were women.

A covariate-adjusted analysis of the matched set found that rituximab-treated patients had a significantly lower EDSS score during a mean follow-up of 3.5 years (mean difference, –0.52). In addition, time to confirmed disability progression was delayed in the rituximab-treated group (hazard ratio, 0.49). "Approximately 75% of untreated and 50% of treated individuals in our cohorts developed clinically significant confirmed progression for the 10-year period," Dr. Naegelin and her colleagues reported. Complications, mainly related to infections, occurred in five cases during treatment. The researchers did not identify major safety concerns, however.

Dr. Naegelin had no conflicts of interest. Several coauthors disclosed research support and compensation from pharmaceutical companies. **NR**

—Jake Remaly

Suggested Reading

Naegelin Y, Naegelin P, von Felten S, et al. Association of rituximab treament with disability progression among patients with secondary progressive multiple sclerosis. *JAMA Neurol.* 2019 Jan 7 [Epub ahead of print].

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Sleep disorders in children with ADHD treated with off-label medications

Medications used to treat ADHD may affect patients' sleep.

Sleep problems in children with attention-deficit/hyperactivity disorder (ADHD) are treated with a variety of medications, many off label for sleep and unstudied for safety and effectiveness in children, a study of Medicaid prescriptions has found.

Tracy Klein, PhD

"Sleep disorders coexist with ADHD for many children and are associated with neuropsychiatric, physiologic, and medication-related outcomes," wrote Tracy Klein, PhD, of Washington State University, Vancouver, and her colleagues. The report is in the *Journal of Pediatric Health Care*. These patients can have sleep disordered breathing and behavioral issues occurring around bedtime. Known adverse effects of the stimulant and nonstimulant medications used to treat ADHD can include sleep disturbance, delayed circadian rhythm, insomnia, and somnolence. Yet, research on sleep problems in children with ADHD and prescribing patterns is scanty, according to the investigators.

> "Developmentally, [children] may be unable to verbally express the side effects they are feeling and may therefore be subject to a drug to treat a drug side effect."

Thirty-day prescriptions

Dr. Klein and her colleagues conducted a study aimed at identifying the off-label medications being prescribed to potentiate sleep in children with ADHD, and the characteristics of the children and their prescribers. They used 5 years of pharmacy claims for children in Oregon who were insured through Medicaid and had a provider diagnosis of ADHD during Jan. 1, 2012, to Dec. 31, 2016. The children were aged 3–18 years, and the researchers assessed the number of 30-day prescriptions for each medication. Prescribers were identified by national provider identifier taxonomies (e.g., nurse, physician, other prescriber), and classified as either generalist or specialist. The medications were classified as controlled or uncontrolled as determined by Title 21 of the U.S. Controlled Substances Act.

The data yielded 14,567 prescriptions for 2,518 children for a 30-day supply of medication known to potentiate sleep but off label for children. Children aged 3–11 years represented about 38% of these patients. Some children were prescribed more than one of these medications. Medications specifically on label for sleep but not indicated for children were not included. Those medications indicated for comorbid conditions and those indicated for ADHD that specifically cause somnolence were excluded.

The uncontrolled medications prescribed in this sample were amitriptyline, doxepin, hydroxyzine, low-dose quetiapine, and trazodone. The controlled medications identified were clonazepam, lorazepam, and phenobarbital.

Most of the prescriptions (63.8%) went to older children aged 12–18 years, and most prescriptions (66.3%) went to males. The most commonly prescribed noncontrolled medication was trazodone (5,190 prescriptions), followed by hydroxyzine (2,539), and quetiapine (2,402). The most frequently prescribed controlled medication was clonazepam (2,145), followed by lorazepam (534).

Specialist prescribers wrote most of the prescriptions for this patient group, but no differences were found in prescribing patterns between specialists and generalists.

Dr. Klein and her colleagues noted that 871 children were prescribed 5,190 30-day–supply prescriptions for trazodone, including 23 children under age 5. Trazodone is a serotonin modulator indicated for the treatment of major depressive disorder, but has not been studied for safety and efficacy in children and has no Food and Drug Administration indication for children. "Hydroxyzine, quetiapine, and amitriptyline also were prescribed for a large number of children, including some for children as young as 3 years, despite lack of approval for use to induce to sleep and increased potential for significant adverse reactions in children," they wrote.

A drug to treat another drug's side effects?

Dr. Klein suggested that prescribers receive pressure from families to "do something" for their children, who may be disruptive day and night. "Prescribers may be unaware that trazodone, which is commonly used in practice, has never been approved for treatment of insomnia in children or adults. Insurance may not adequately fund other options, such as extensive behavioral therapy," she stated in an interview. These medications come with some risk for children, Dr. Klein noted.

"Developmentally, [children] may be unable to verbally express the side effects they are feeling and may therefore be subject to a drug to treat a drug side effect, especially if their reaction to it is behavioral." There is also potential for unanticipated drug interactions between off-label medications prescribed for sleep and drugs prescribed to treat ADHD.

This study has limitations related to the absence of detailed clinical explanatory information found in claims data. Information on adherence to treatment and adverse events, for example, is not contained in claims data. The study does not address the overall rates of sleep disorders in children with ADHD nor the percentage of children with ADHD who are prescribed any medication to potentiate sleep, but looks at which off-label drugs are being prescribed, to which children, and by whom.

"Most medications prescribed in this study, used to induce sleep or treat insomnia, have not been studied for safety and efficacy in children, and their use should not be extrapolated from adult studies," the researchers concluded.

The research team reported no conflicts of interest. **NR**

—Therese Borden

Suggested Reading

Klein T, Woo TM, Panther S, et al. Somnolence-producing agents: a 5-year study of prescribing for Medicaid-insured children with attention deficit hyperactivity disorder. *J Pediatr Health Care*. 2019 Jan 7 [Epub ahead of print].

Food allergies are associated with MS relapses and lesions

The biologic mechanisms of these associations, which are unknown, could become targets for therapeutic strategies.

Patients with multiple sclerosis (MS) and food allergies have more relapses and a higher likelihood of gadolinium-enhancing lesions than patients with MS but no food allergies, according to an analysis published online ahead of print December 18, 2018, in *Journal of Neurology, Neurosurgery and Psychiatry*.

Patients with food allergies had a 1.3-times higher cumulative number of attacks and a 2.5-times higher likelihood of gadolinium-enhancing lesions on brain MRI in the analysis of data from the Comprehensive Longitudinal Investigation of MS at the Brigham and Women's Hospital (CLIMB).

By contrast, there were no significant differences in relapse or lesion rates for patients with environmental or drug allergies, compared with patients without allergies, said Tanuja Chitnis, MD, director of Partners Pediatric MS Center at the Massachusetts General Hospital for Children in Boston, and her coinvestigators. "Our findings suggest that MS patients with allergies have more active disease than those without allergies, and that this effect is driven by food allergies," said the researchers.

Previous investigations examining whether allergy history increases the risk of developing MS have yielded conflicting results, they added. A meta-analysis of 10 observational studies did not support an association between allergic diseases and MS risk.

By contrast, the question of whether allergies lead to more or less intense MS activity has not been addressed, according to the investigators. Theirs is the first study to assess the relation between allergy and MS disease course using clinical and MRI variables, they said.

Allergy status based on self-report

The study examined 1,349 patients with MS who were enrolled in CLIMB and completed a self-administered questionnaire on food, environmental, and drug allergies. Of those patients, 922 reported allergies, while 427 reported no known allergies.

After adjustments for gender, age at symptom onset, disease category, and time on treatment, patients with food allergies had a significantly increased cumulative number of attacks, compared with those with no allergies (relapse rate ratio, 1.274). Patients with food allergies were more than twice as likely as patients without these allergies to have gadolinium-enhancing lesions on brain MRI after adjusting for other covariates (odds ratio, 2.53).

Patients with environmental and drug allergies also appeared to have more relapses, compared with patients with no allergies, in univariate analysis, but the differences were not significant in the adjusted analysis. Likewise, patients with environmental or drug allergies tended to be more likely to have new lesions than those without these allergies, but this trend was not observed in the multivariate analysis.

The potential role of gut microbiota

The underlying biologic mechanisms that link food allergies with MS disease severity are unknown. Experimental studies support the hypothesis that gut microbiota might affect the risk and course of MS, said Dr. Chitnis and her coauthors.

The CLIMB study was supported by Merck Serono and the National MS Society Nancy Davis Center Without Walls. Dr. Chitnis reported receiving consulting fees from Biogen Idec, Novartis, Sanofi, Bayer, and Celgene outside the submitted work. Coauthors provided additional disclosures related to Merck Serono, Genentech, Verily Life Sciences, EMD Serono, Biogen, Teva, Sanofi, and Novartis, among others. **NR**

—Andrew D. Bowser

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Fakih R, Diaz-Cruz C, Chua AS, et al. Food allergies are associated with increased disease activity in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2018 Dec 18 [Epub ahead of print].

Patients with HIV may have neuromyelitis optica spectrum disorder

All patients with HIV infection and optic neuritis or myelitis should have their anti–aquaporin 4 antibody status checked.

HIV-associated neuromyelitis optica spectrum disorder (NMOSD) is a recently recognized entity, and a high index of suspicion is needed to diagnose this disorder, according to Thomas Mathew, MD, and his colleagues at St. John's Medical College Hospital in Bengaluru, India.

"NMOSD can be associated with a wide range of autoimmune diseases, but clinicians rarely diagnose NMOSD in cases of HIV infection, and HIV-associated NMOSD is rarely mentioned in the conventional classification of NMOSD," they stated.

Dr. Mathew and his colleagues reported the results of a study of six cases of HIV-NMOSD identified from the literature and 1 HIV-infected patient from a registry for NMOSD that they had established, which had a total of 25 patients with the condition.

There were four males and three females in the study, ranging from 8 years to 49 years of age. The duration of HIV infection in these patients ranged from newly detected to 15 years, according to the report, which was published in the January issue of *Multiple Sclerosis and Related Disorders*.

Optic neuritis followed by myelitis, the most common presentation, occurred in five of the seven patients. Of these, six patients were assayed for anti–aquaporin 4 antibodies, which are considered a serological marker of neuromyelitis optica; three patients were positive and three were negative.

All patients received immunomodulatory treatment. Five of the seven patients had a poor recovery from acute attacks, but no patient had further relapses while on immunomodulatory treatment and antiretroviral therapy.

Dr. Mathew and his colleagues suggested that all patients with HIV infection presenting with optic neuritis or myelitis should have their anti–aquaporin 4 antibody status checked. He recommended that in all patients with NMOSD, HIV infection be ruled out.

"The prognosis of these patients is variable; residual neurological deficits were common, but treatment prevented further attacks. Increased awareness of this association will lead to earlier diagnosis, early treatment, and prevention of disability," the researchers concluded.

The authors reported that they had no conflicts of interest. **NR**

—Mark S. Lesney

Suggested Reading

Mathew T, Avati A, D'Souza D, et al. HIV infection associated neuromyelitis optica spectrum disorder: clinical features, imaging findings, management and outcomes. Mult Scler Relat Disord. 2019;27:289-293.

Dabigatran matches aspirin for second stroke prevention

In RE-SPECT ESUS, dabigatran proves no better than aspirin for preventing a second stroke after an embolic stroke of undetermined source.

MONTREAL—For the second time in a year, an anticoagulant failed to show superiority when it was compared with aspirin for preventing a second stroke in patients who had had an index embolic stroke of undetermined source (ESUS). But the most recent results gave a tantalizing suggestion that the anticoagulant approach might be effective for older patients, those at least 75 years old, possibly because these patients have the highest incidence of atrial fibrillation (AF).

"The fact that we saw a treatment benefit in patients 75 and older [in a post hoc, subgroup analysis] means that development of AF is probably the most important factor," Hans-Christoph Diener, MD, said at the World Stroke Congress. Another clue that incident AF drove a treatment benefit hidden in the new trial's overall neutral result was that a post hoc, landmark analysis showed that while the rate of second strokes was identical during the first year of follow-up in patients on either aspirin or the anticoagulant dabigatran (Pradaxa) after an index ESUS, patients on dabigatran had significantly fewer second strokes during subsequent follow-up.

More follow-up time was needed to see a benefit from anticoagulation because "it takes time for AF to develop, and then once a patient has AF, it takes time for a stroke to occur," explained Dr. Diener, professor of neurology at the University of Duisburg-Essen in Essen, Germany.

Trial design

The RE-SPECT ESUS (Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source) trial randomized 5,390 patients at more than 500 sites in 41 countries, including the United States, within 6 months of an index ESUS who had no history of AF and no severe renal impairment. All enrollees had to have less than 6 minutes of AF episodes during at least 20 hours of cardiac monitoring, and they had to be free of flow-limiting stenoses (50% or more) in arteries supplying their stroke region. Patients received either 150 mg or 110 mg of dabigatran twice daily, depending on their age and renal function, or 100 mg of aspirin daily. About a quarter of patients randomized to dabigatran received the lower dosage. The enrolled patients averaged 66 years old, almost two-thirds were men, and they started treatment a median of 44 days after their index stroke.

During a median 19 months' follow-up, the incidence of a second stroke of any type was 4.1% per year among the patients on dabigatran and 4.8% per year among those on aspirin, a difference that was not statistically significant. However, the post hoc landmark analysis showed a significant reduction in second strokes with dabigatran treatment after the first year. In addition, a post hoc subgroup analysis showed that, among patients aged at least 75 years old, treatment with dabigatran was linked with a statistically significant 37% reduction in second strokes, compared with treatment with aspirin, Dr. Diener reported.

> "A treatment benefit in patients 75 and older means that development of AF is probably the most important factor."

Safety analysis

The primary safety end point was major bleeds, as defined by the International Society on Thrombosis and Haemostasis, which occurred in 1.7% per year of patients on dabigatran and 1.4% per year of those on aspirin, a difference that was not statistically significant. Patients on dabigatran had a significant excess of major bleeds combined with clinically significant nonmajor bleeds: 3.3% per year versus 2.3% per year among those on aspirin.

Hans-Christoph Diener, MD

A little over 4 months before Dr. Diener's report, a separate research group published primary results from the NAVIGATE ESUS (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source) trial, which compared the anticoagulant rivaroxaban (Xarelto) with aspirin for prevention of a second stroke in 7,213 ESUS patients. The results showed no significant efficacy difference between rivaroxaban and aspirin.

RE-SPECT ESUS was funded by Boehringer Ingelheim, the company that markets dabigatran. Dr. Diener has been a consultant to and has received research funding from Boehringer Ingelheim, as well as several other companies. **NR**

—Mitchel L. Zoler

Suggested Reading

Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med.* 2018;378(23):2191-2201.

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Nuedexta is mostly prescribed to off-label populations

Approximately 15% of patients had multiple sclerosis or amyotrophic lateral sclerosis, the diagnoses of patients in the pivotal trial.

Approximately 15% of patients prescribed dextromethorphan–quinidine (Nuedexta) have pseudobulbar affect due to multiple sclerosis (MS) or amyotrophic lateral sclerosis (ALS), the condition for which this drug is indicated, according to an analysis of two national commercial insurance claims databases published online ahead of print January 7 in *JAMA Internal Medicine*. About 57% of patients prescribed dextromethorphan–quinidine have Parkinson's disease or dementia.

The number of prescriptions for dextromethorphan–quinidine rose 15-fold during a recent 6-year period, with a concurrent 50-fold rise in reimbursement, according to Medicare Part D data. "In response to findings such as ours, further attention should be paid to educating prescribers about the actual benefits and risks of this costly drug combination," said Michael Fralick, MD, a research fellow at Brigham and Women's Hospital and Harvard Medical School in Boston, and coauthors.

Insurance claims analyzed

The Food and Drug Administration approved Nuedexta in 2010 for the treatment of pseudobulbar affect after it produced modest improvements in laughing or crying episodes in a 12-week, placebo-controlled trial of patients with MS or ALS. The initial FDA label noted, "Nuedexta has not been shown to be safe or effective in other types of emotional lability that can commonly occur, for example, in Alzheimer's disease and other dementias." In 2015, patients with Alzheimer's disease had modest improvements in agitation scores when they received dextromethorphan–quinidine in a 10-week, placebo-controlled, industry-designed and -sponsored trial. Although the dextromethorphan–quinidine arm also had higher rates of falls, urinary tract infections, and serious adverse events, the prescribing information was updated in 2015 to remove the statement about patients with dementia.

> "In response to findings such as ours, further attention should be paid to educating prescribers about the actual benefits and risks of this costly drug combination."

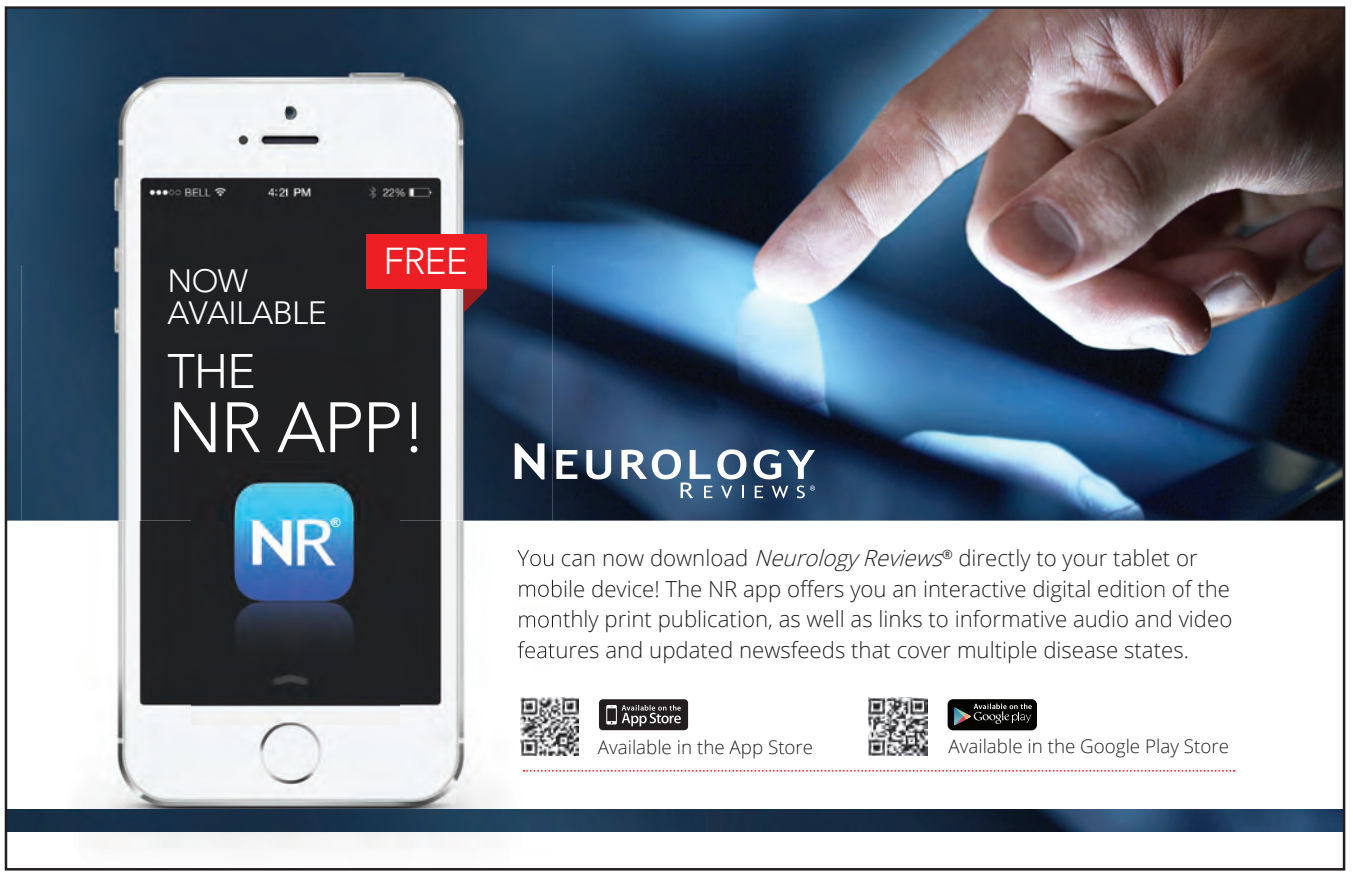
To assess prescribing patterns for dextromethorphan–quinidine, Dr. Fralick and his colleagues analyzed data from 12,858 patients who filled prescriptions for this medication between 2010 and 2017 that were recorded in the Optum Clinformatics Data Mart or Truven Health MarketScan databases. Overall, 8.4% of patients had MS, and 6.8% had ALS, while 57% had dementia or Parkinson's disease, and 28% had an unknown diagnosis. The number of patients prescribed dextromethorphan–quinidine increased from 3,296 in 2011 to 50,402 in 2016. Spending on this medication by the Centers for Medicare & Medicaid Services increased from $3.9 million to $200.4 million during the same period.

Off-label treatment entails risks

Current treatments for behavioral symptoms of dementia "are largely ineffective, and thus clinicians may want to prescribe dextromethorphan–quinidine to see if it helps their patients. ... Yet the absence of data showing efficacy, coupled with the demonstrated risks of falls and possible cardiac effects, calls this strategy into question," said the researchers. "Further studies should be required to evaluate the safety and effectiveness of this medication as it is currently being used."

Study funders included the Laura and John Arnold Foundation, the Harvard Program in Therapeutic Science, the Engelberg Foundation, and the University of Toronto Clinician Scientist Training Program. One author disclosed grants from the FDA Office of Generic Drugs and Division of Health Communication unrelated to the study topic. **NR**

—Amy Karon



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Frontal lobe epilepsy elevates seizure risk during pregnancy

About 53% of women with frontal lobe epilepsy have increased seizure frequency during pregnancy.

NEW ORLEANS—Seizure frequency increased during pregnancy for 53% of women with frontal lobe epilepsy, based on a study reported by Paula E. Voinescu, MD, PhD, at the annual meeting of the American Epilepsy Society.

The single-center study included data on 76 pregnancies in women with focal epilepsy—17 of them in patients with frontal lobe epilepsy—and 38 pregnancies in women with generalized epilepsy. Seizures were more frequent during pregnancy, compared with baseline, in 5.5% of women with generalized epilepsy, 22.6% of women with focal epilepsies, and 53.0% of women with frontal lobe epilepsy, said Dr. Voinescu, lead author of the study and a neurologist at Brigham and Women's Hospital in Boston.

"Frontal lobe epilepsy is known to be difficult to manage in general and often resistant to therapy, but it isn't clear why the seizures got worse among pregnant women, because the levels of medication in their blood was considered adequate. Until more research provides treatment guidance, doctors should carefully monitor their pregnant patients who have focal epilepsy to see if their seizures increase despite adequate blood levels and then adjust their medication if necessary," she advised. "As we know from other research, seizures during pregnancy can increase the risk of distress and neurodevelopmental delays for the baby, as well as the risk of miscarriage."

For the study, Dr. Voinescu and her colleagues analyzed prospectively collected clinical data from 99 pregnant women followed at Brigham and Women's Hospital between 2013 and 2018.

The researchers excluded patients with abortions, seizure onset during pregnancy, poorly defined preconception seizure frequency, nonepileptic seizures, antiepileptic drug (AED) noncompliance, and pregnancies that were enrolled in other studies. The investigators documented patients' seizure types and AED regimens and recorded seizure frequency during the 9 months before conception, during pregnancy, and 9 months post partum. The researchers summed all seizures for each individual for each interval. They defined seizure frequency worsening as any increase above the preconception baseline, and evaluated differences between focal and generalized epilepsy and between frontal lobe and other focal epilepsies.

Increased seizure activity tended to occur in women on more than one AED, according to Dr. Voinescu. In women with frontal lobe epilepsy, seizure worsening during pregnancy was most likely to begin in the second trimester.

The gap in seizure frequency between the groups narrowed in the 9-month postpartum period. Seizures were more frequent during the postpartum period, compared with baseline, in 12.12% of women with generalized epilepsy, 20.14% of women with focal epilepsies, and 20.00% of women with frontal lobe epilepsy.

Future analyses will evaluate the influence of AED type and concentration and specific timing on seizure control during pregnancy and the postpartum period, Dr. Voinescu said. Future studies should also include measures of sleep, which may be a contributory mechanism to the differences found between these epilepsy types.

Dr. Voinescu reported receiving funding from the American Brain Foundation, the American Epilepsy Society, and the Epilepsy Foundation through the Susan Spencer Clinical Research Fellowship. **NR**

—Jake Remaly

Onset of pediatric status epilepticus may have a circadian pattern

Onset of refractory pediatric status epilepticus may peak between 10 a.m. and 11 a.m.

NEW ORLEANS—The onset of pediatric refractory status epilepticus follows a circadian pattern, according to research presented at the annual meeting of the American Epilepsy Society. The number of episodes is greatest between 10 a.m. and 11 a.m. and smallest between 10 p.m. and 11 p.m.

"Our findings may inform the increase in preventive monitoring, such as video monitoring or seizure-tracking devices for patients," said Justice Clark, MPH, a program coordinator at Boston Children's Hospital. "They may also inform chronotherapeutic strategies."

Research suggests that various types of seizures cluster at different times of the day. Data about the circadian distribution of status epilepticus, however, are limited.

Ms. Clark and colleagues conducted a prospective observational study at 25 hospitals in the United States and Canada from June 2011 to January 2018. Eligible participants were between ages 1 month and 21 years, had focal or generalized convulsive status epilepticus, and had failed to respond to one benzodiazepine and one nonbenzodiazepine antiseizure medication. For patients with more than one episode of refractory status epilepticus during the study, the researchers included only the first episode.

The investigators examined whether the temporal distribution of pediatric refractory status epilepticus onset followed a circadian pattern using a cosinor analysis with a 12-hour cycle. They used the midline-estimating statistic of rhythm (MESOR) technique to estimate the mean number of refractory status epilepticus episodes per hour if onset was evenly distributed. The amplitude in this analysis was the difference in number of episodes per hour between the MESOR and the peak or the MESOR and the trough.

Ms. Clark and her colleagues included 300 patients in their analysis, each of whom had one episode. Approximately 45% of participants were female. The population's median age was 4.2 years, and the median duration of status epilepticus was 120 minutes.

The MESOR was 12.5 episodes per hour, and the amplitude was 2.4 episodes per hour, indicating that the distribution was not even over 24 hours. The peak number of onsets was between 10 a.m. and 11 a.m., and the trough was between 10 p.m. and 11 p.m.

A secondary analysis examined the circadian distribution of time to treatment with rescue medications. The distribution of time to treatment with the first benzodiazepine did not differ significantly from a uniform distribution. The time to treatment with the first nonbenzodiazepine antiseizure medication, however, was not uniformly distributed. The longest time to treatment occurred between 3 a.m. and 4 a.m., and the shortest time was between 3 p.m. and 4 p.m. "Although fewer refractory status epilepticus episodes occurred at night, the time to antiseizure medication administration was the longest [during that period]. Thus, nighttime refractory status epilepticus episodes may be at higher risk for delayed treatment," said Ms. Clark. A limitation of this analysis is that it was influenced by outliers, she added.

The Pediatric Epilepsy Research Foundation and the Epilepsy Research Fund supported the study. **NR**

—Erik Greb

Self-management program decreases seizure frequency

The program also may reduce depression and improve function and quality of life.

NEW ORLEANS—A self-management program that focused on medication adherence, sleep, nutrition, and stress reduction was associated with decreased seizures and improved quality of life for adults with epilepsy.

SMART (Self-Management for People With Epilepsy and a History of Negative Health Events) also was associated with improved depression scores and overall quality of life measures, compared with a wait-list control, Martha Sajatovic, MD, said at the annual meeting of the American Epilepsy Society.

"I believe what we're seeing is a result of improved self-management," said Dr. Sajatovic, the Willard Brown Chair in Neurological Outcomes Research at Case Western Reserve University, Cleveland. "This is multimodal, including better medication adherence, which in turn is related to better communication with the clinician. For example, if patients are not sleeping well or their medicine makes them nauseated or they experience sexual dysfunction, we encourage them to talk to their docs about what they can live with and what they can't."

> SMART is an 8-week online educational program delivered by a nurse educator and a peer educator with epilepsy.

Presented as a poster during the meeting, the SMART study was also published in *Epilepsia*.

SMART is an 8-week online educational program delivered by a nurse educator and a peer educator with epilepsy who has had at least three negative health events. The first session is an in-person visit during which the team gets acquainted and discusses goals. The remaining sessions are self-paced and delivered on computer tablets provided by the investigators.

SMART didn't just focus on the physical issues of living with epilepsy, Dr. Sajatovic said in an interview. Sessions also discussed the stigma still associated with the disorder and myths that unnecessarily inflate perceptions. Discussions include goal setting, epilepsy complications and how to manage them, the importance of good sleep hygiene, problem-solving skills, nutrition and substance abuse, exercise, and how to deal with medication side effects.

"One thing we really stressed was sharing information in a way that was accessible to all patients and fostered self-motivation," she said. "Most of

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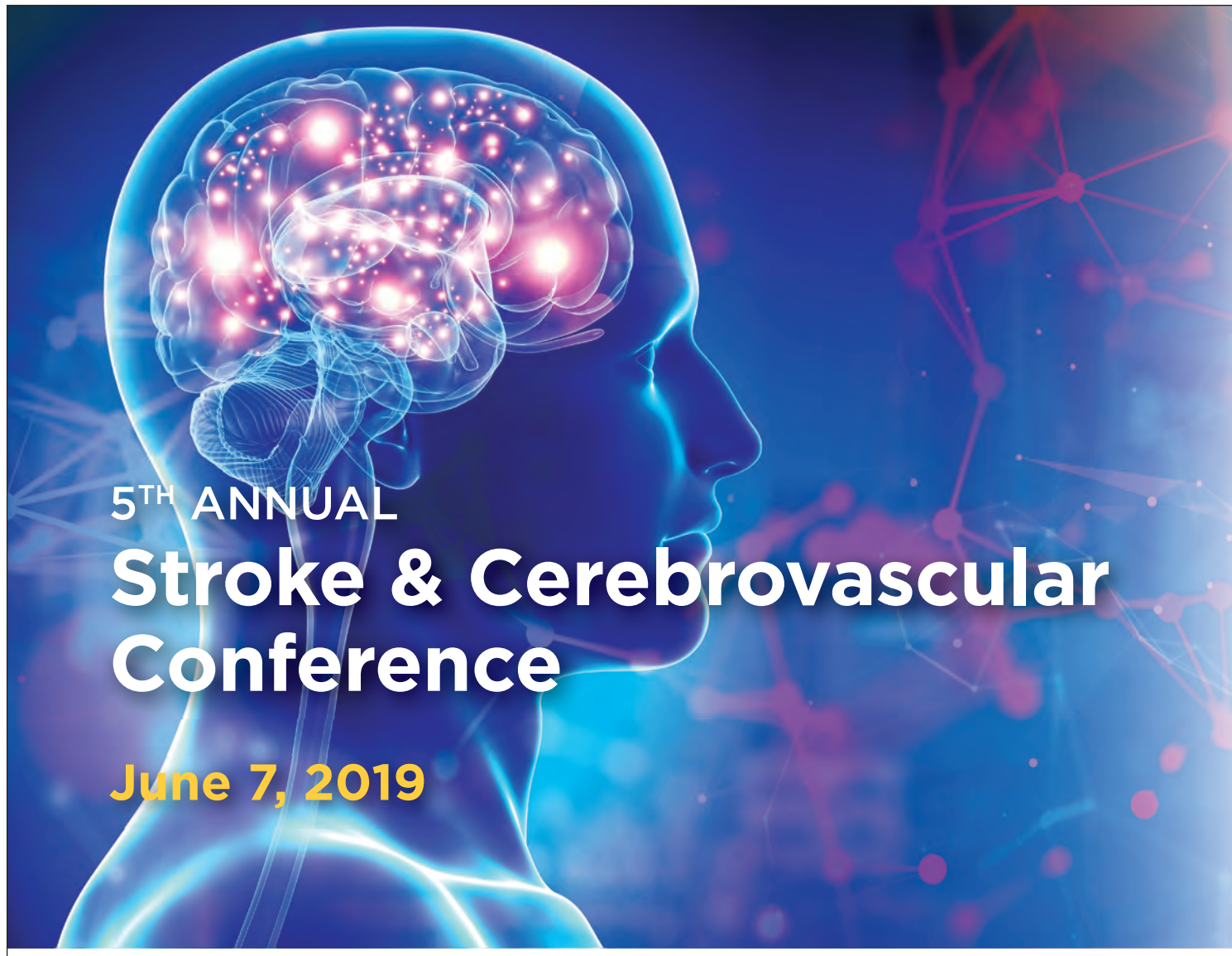

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Participants in a self-management program had less depression, better function, and improved quality of life

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our participants had never been in a program like this before. It was very empowering for many."

The researchers chose participants who were socioeconomically challenged for this project; 88% made less than $25,000 per year, and 74% were unemployed. The mean age of participants was 41 years, 70% were black, and most had been living with epilepsy for at least half of their life. About 70% lived alone, and 70% had experienced at least one seizure within the month before enrolling. Mental health comorbidities were common; 69% had depression, 32% had anxiety, and 13% had PTSD.

The study enrolled 120 people who were evenly divided between the intervention group and the wait-list group. The primary outcome was the change in total negative health events from baseline to the study's end. Negative health events were seizures and emergency department or hospital admissions for any other causes, including attempts at self-harm, falls, and accidents.

Secondary outcomes included changes in depression scores as measured by the Montgomery-Åsberg Depression Rating Scale and the 9-item Patient Health Questionnaire. Quality of life was measured using the 10-item Quality of Life in Epilepsy. Functional status was measured using the 36-Item Short-Form Health Survey.

At baseline, the total mean 6-month negative health events count was 15, with 13 events being seizures. The other events were hospital or emergency department visits for other reasons.

At the end of the study, the intervention group experienced a significant mean decrease of 10 negative health events, compared with a decrease of 2 in the wait-listed group. This result was largely driven by a mean of 7.8 fewer seizures in the active group, compared with a decrease of about 1.0 in the wait-listed group. The 6-month emergency department and hospitalization counts did not significantly change.

Among the secondary outcomes, depression, overall health, and quality of life improved significantly in the intervention group, compared with the wait-listed group. The intervention group also had significant decreases in depression measures and improvements in daily function measures, Dr. Sajatovic said.

"It was so gratifying to see this. Most of our participants had never been in a program like this before. It was a chance for them to take control of their epilepsy instead of simply having it control them," she said.

This study was supported by a grant from the Centers for Disease Control and Prevention. Dr. Sajatovic had no financial disclosures related to this presentation. **NR**

—Michele G. Sullivan

Martha Sajatovic, MD

Suggested Reading

Sajatovic M, Colon-Zimmermann K, Kahriman M, et al. A 6-month prospective randomized controlled trial of remotely delivered group format epilepsy self-management versus wait-list control for high-risk people with epilepsy. *Epilepsia.* 2018;59(9):1684-1695.

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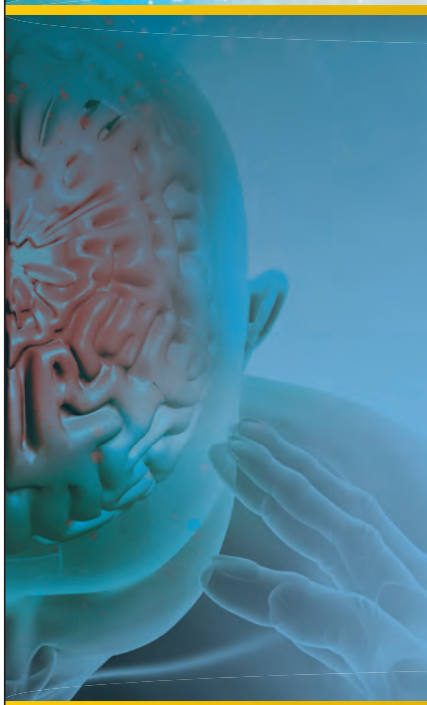

Nasal Spray for Acute Migraine Care in Adults and Adolescents

ALAN RAPOPORT, MD

STEWART TEPPER, MD

In this supplement to *Neurology Reviews*, Alan Rapoport, MD, and Stewart Tepper, MD, share an overview of available treatment options for acute migraine care, including a nasal spray formulation approved for use in adult and adolescent patients.*

TOPICS INCLUDE:

- Importance of triptans in the acute migraine care space
- Use of a nasal spray formulation in the treatment of acute migraine
- Safety and efficacy in adult and adolescent migraine patients

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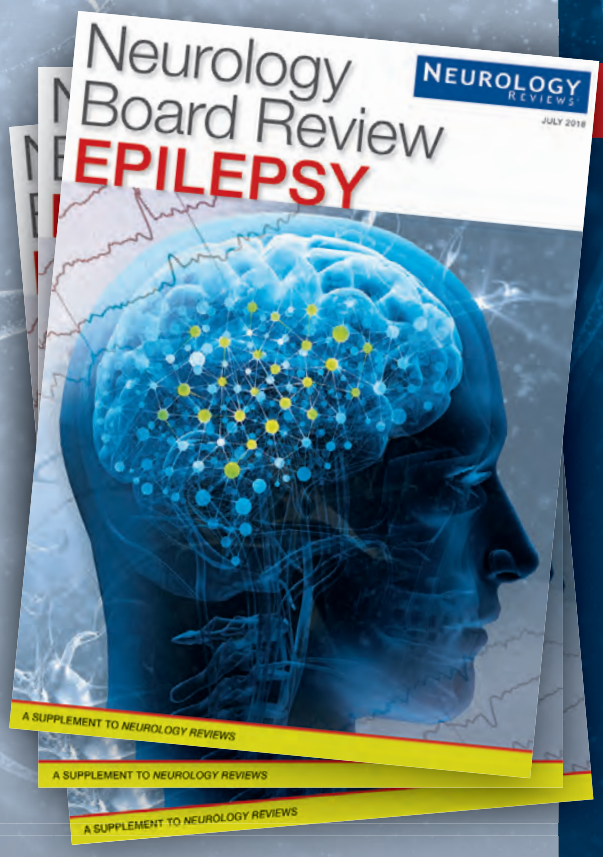

NEW! A special supplement to *Neurology Reviews*

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Excessive and insufficient sleep are associated with atherosclerosis

The sleep duration considered optimal is between 7 and 8 hours per night.

Too little sleep, too much sleep, and fragmented sleep are independently associated with increased subclinical, noncardiac atherosclerotic plaque in healthy middle-aged men and women, according to a Spanish investigation of bank employees.

"Overall, our findings support the potential role of healthy sleeping in protecting against atherosclerosis. Thus, recommending good sleep hygiene [i.e., 7–8 hours per night] should be part of the lifestyle modifications provided in our daily clinical practice," said Fernando Domínguez, MD, PhD, of Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) in Madrid, and colleagues. The study was published in the January issue of *Journal of the American College of Cardiology*.

> "Recommending good sleep hygiene should be part of the lifestyle modifications provided in daily clinical practice."

Accelerometers recorded sleep duration

Previous studies have found associations between sleep problems and increased cardiovascular risk, but the investigations tended to focus on patients with obstructive sleep apnea (OSA) and other problems and often relied on patient self-report. The investigators wanted to use an objective measure to examine whether the relationship is seen in healthy adults.

The participants had no known cardiovascular disease and wore Acti Trainers accelerometers (Actigraph, Pensacola, Fla.) around their waists for 7 days to record sleep duration and quality. Subjects also had their plaque burdens assessed by 3-dimensional vascular ultrasound (VUS) at their carotid and femoral arteries bilaterally. Cardiac CT was used to assess coronary artery calcification as a surrogate for coronary artery atherosclerosis.

Sleep fragmentation was associated with plaques at multiple sites

The 3,974 participants had a mean age of 46 years, and a third were women. Participants had a low prevalence of hypertension and diabetes. OSA patients were excluded from the study. Overall, 27% had very short sleep duration (VSSD), which was defined as less than 6 hours per night. Approximately 38% of participants had short sleep duration (SSD), 31% slept from 7 to 8 hours per night, and 4% had long sleep duration (LSD), defined as greater than 8 hours per night. Participants who slept for 7–8 hours per night served as the reference group for healthy sleep habits.

After adjustment for cardiovascular risk factors, including body mass index, hypertension, and smoking, VSSD was independently associated with a higher atherosclerotic burden, compared with the reference group (odds ratio [OR], 1.27; 95% confidence interval [CI], 1.06–1.52; $P = 0.008$). Participants in the highest quintile of sleep fragmentation were more likely to have plaques at multiple sites (OR, 1.34; 95% CI, 1.09–1.64; $P = 0.006$). The Framingham risk score at 10 and 30 years was significantly higher in participants with VSSD or SSD and in the highest quintiles of sleep fragmentation.

LSD was significantly associated with a higher plaque burden in women. "Too-long sleep duration may not be healthy, either. Recommendations should be restricted to 7 to 8 hours," the investigators said.

Sleep duration and quality were not associated with inflammation markers or coronary artery calcification. The investigators noted that CT for coronary artery calcification might not be as sensitive as VUS for identifying subclinical atherosclerosis.

Short sleepers tended to have higher intake of alcohol and caffeine than did those who slept for 7–8 hours.

The work was funded by CNIC and Banco Santander, among other entities. Dr. Domínguez had no disclosures. Investigator Hector Bueno, MD, PhD, reported research funding and fees from several companies, including AstraZeneca and Novartis. The second author, Valentín Fuster, MD, PhD, is the editor of the *Journal of the American College of Cardiology,* which published the report.

A prospective cardiovascular sleep study is warranted

This study extends the published reports on sleep duration and vascular disease to an early middle-aged cohort by using an objective measure of sleep duration and sensitive measures of atherosclerosis in multiple vascular territories, said Deepak Bhatt, MD, professor of cardiovascular medicine, and Daniel Gottlieb, MD, an associate professor of medicine, both of Harvard Medical School in Boston, in an accompanying editorial.

Ultimately, studies of sleep extension are needed to determine whether modification of sleep behaviors will improve vascular health outcomes. The potentially enormous impact of sleep deprivation and disruption on population health, reinforced by the present study, is ample justification for such trials, which are needed to place sleep with confidence alongside diet and exercise as a key pillar of a healthy lifestyle, said Drs. Bhatt and Gottlieb.

However, hypertension and diabetes were more common in the group sleeping fewer than 6 hours per night, but neither blood pressure nor glucose metabolism was assessed with sufficiently comprehensive measures to explore these factors as potential effect mediators.

More importantly, the causes of short sleep duration and sleep fragmentation in this cohort are unknown. It is unclear to what extent short sleep duration in this cohort reflects voluntary behaviors that limit time available for sleep versus insomnia. Insomnia is itself associated with increased risk of vascular disease, the authors concluded.

Dr. Bhatt reported research funding and income from several companies, including Abbott, Boehringer Ingelheim, and Medtronic. **NR**

—M. Alexander Otto

Suggested Reading

Domínguez F, Fuster V, Fernandez-Alvira JM, et al. Association of sleep duration and quality with subclinical atherosclerosis. *J Am Coll Cardiol.* 2019;73(2):134-144.

Gottlieb DJ, Bhatt DL. More evidence that we could all use a good night's sleep. *J Am Coll Cardiol.* 2019;73(2):145-147.

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