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INSIDE

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Are Vaccines Safe after Guillain-Barré and Chronic Inflammatory Demyelinating Neuropathy?

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports no financial relationships relevant to this field of study.

Synopsis: *Vaccines appear to be safe for patients who have been previously diagnosed with GBS or CIDP, and are recommended in appropriate individuals.*

Source: Kuitwaard K, et al. Recurrences, vaccinations and long-term symptoms in GBS and CIDP. *J Peripher Nerv Syst* 2009; 14:310-315.

Is it safe to vaccinate a patient with a prior history of Guillain-Barré syndrome (GBS) or chronic inflammatory demyelinating polyneuropathy (CIDP)? What is the likelihood of recurrence of GBS even in the absence of vaccination, and what are the long-term consequences of inflammatory demyelinating polyneuropathy? To address these questions, all members of the Dutch Society of Neuromuscular Disorders were sent a set of questionnaires in June 2008, followed by two reminder letters to improve response rates, asking them to reply if they had a diagnosis of GBS, Miller Fisher syndrome, or CIDP. Issues addressed by the questionnaires encompassed prior vaccinations, family history of GBS or CIDP, presence of other autoimmune diseases, and persistent symptomatology. Also included were the short-form (SF-36) health survey, and standardized sub-questionnaires related to pain, fatigue, anxiety, and depression. Statistical analysis comprised the chi-square test, Fisher exact test, Mann-Whitney U test or t-test, and Spearman's correlation coefficient (r_s), with a $p < 0.05$ considered significant.

Of 461 members who received the mailings, 323 responded, two of whom were excluded due to incorrect or lack of diagnosis. Of the remaining 321 patients, 76 had CIDP, and 245 had GBS,

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four of whom had Miller Fisher syndrome, five had an overlap of Miller Fisher syndrome and GBS, and one had Bickerstaff's encephalitis. Recurrent GBS was reported in 19 patients but could only be confirmed in nine (4%). Immune-mediated polyneuropathy was reported in a family member in eight GBS patients, six of whom had GBS, and one each had CIDP or multifocal motor neuropathy. A single CIDP patient had a grandson with CIDP. Autoimmune disease, usually thyroid, was reported in 23 (9%) and four (5%) patients with GBS and CIDP, respectively. Prior vaccination, usually for the flu, was reported in 23 GBS (9%) and eight (11%) CIDP patients within eight weeks prior to disease onset, but none of 106 GBS patients who were vaccinated (range 1–37 times, total 775 vaccinations) subsequent to their GBS experienced a recurrence. Among 24 CIDP patients who received vaccines (range 1–17 times) following their CIDP, five reported increased symptomatology. Long after diagnosis, pain was reported in 71% and 72% of GBS and CIDP patients, respectively, and it was felt to be severe in 8% and 17 %, respectively. Even years following diagnosis, fatigue was reported in 45% and 25% of GBS and CIDP patients, respectively. Although patients with prior GBS or CIDP continue to experience pain and fatigue long after diagnosis, seasonal vaccination of these patients, particularly GBS, appears to carry a low risk of recurrence.

■ COMMENTARY

Review of the peer-reviewed literature between 1950 and 2008 supports the notion that vaccinations are only rarely associated with subsequent development of Guillain-Barré syndrome (Haber P, et al. *Drug Safety* 2009;32;309-323). With the exception of the swine flu vaccine used in 1976–1977, which carries the strongest causal association, such influenza vaccine associations as have been reported appear to be temporal, rather than causal. Current formulations of rabies vaccine, derived from chick embryo cells, are similarly not associated with a greater than expected rate of GBS. No correlation has been confirmed between GBS and oral polio vaccine or tetanus toxoid-containing vaccines, and reported associations of GBS following quadrivalent conjugated meningococcal vaccine (MCV4) lack controlled epidemiological studies and remain inconclusive. From all available data, it appears that the benefits of vaccination outweigh the risks. ■

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Questions & Comments

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Will Injection Therapy Soon Be Obsolete for Patients with Multiple Sclerosis?

ABSTRACT & COMMENTARY

By Susan Gauthier, DO, MS

Assistant Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Gauthier reports no financial relationships relevant to this field of study.

Synopsis: *Three phase III clinical trials of two oral agents for the treatment of multiple sclerosis were found to have a beneficial effect on clinical and MRI markers of disease activity, but there is a heightened concern for long-term safety due to cases of malignancy reported in each of the three studies.*

Sources: Kappos L, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010:362;5; Cohen J, et al. Oral fingolimod or interferon for relapsing multiple sclerosis. *N Engl J Med* 2010:362;5; Giovannoni G, et al. The CLARITY Study Group. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med* 2010;362:416-426.

THE PRESENT CATEGORIES OF THERAPY USED TO TREAT multiple sclerosis (MS), which include anti-inflammatory, immune modulator, and immunosuppressant, have overlapping immunological effects and therefore are not absolutely distinct. The currently available

injectable therapies, which include glatiramer acetate and interferon beta, are considered immune modulating treatments (IMT). These agents are only partially effective, thus immunosuppressant agents have been traditionally used for patients failing IMT treatment. In general, therapies considered to be immunosuppressant have directed intracellular mechanisms, which involve DNA synthesis and/or immune cell activation, primarily targeted within the bone marrow and other lymphoid organs. The most widely studied agents in MS include cyclophosphamide and mitoxantrone; however, given the variety of toxicities, their use is limited. Natalizumab, a monoclonal antibody against α_4-integrin, differs from standard immunosuppressant therapy, as it binds to specific extracellularly expressed molecules. However, given the risk of progressive multifocal encephalopathy associated with natalizumab, its use has also been limited.

Three recent phase III studies of two new oral agents for the treatment of relapsing MS have introduced novel approaches to immunosuppressant therapy in MS. Fingolimod, a sphingosine-1-phosphate receptor modulator, binds to sphingosine-1-phosphate type 1 receptor in its phosphorylated form and induces receptor internalization; this process ultimately renders activated lymphocytes incapable of migrating out of the lymphoid tissues. Low (0.5 mg) and high (1.25 mg) daily doses of fingolimod were tested in two separate studies. The FREEDOMS study was placebo-controlled over two years and the TRANSFORMS study was a one-year comparative study against intramuscular interferon beta-1a. In the FREEDOMS study, the relative reduction in relapse rate for low- and high-dose fingolimod was 54% and 60%, respectively. Regarding secondary endpoints, both doses of fingolimod reduced the risk of sustained disability over 24 months and decreased magnetic resonance imaging (MRI) measures of inflammation. Interestingly, the rate of brain volume loss was slower in fingolimod treated patients. In the TRANSFORMS study, there was a relative reduction in relapse rate of 52% and 38% for low- and high-dose fingolimod, respectively, as compared to intramuscular interferon beta-1a. There was no difference in disability (EDSS), although the MRI results were favorable to fingolimod. Given the presence of sphingosine receptions on cardiac myocytes, transient bradycardia and first- and second-degree heart block was observed in fingolimod treated patients and was partially dose-related. Similarly, macular edema was more common in the higher dose and stabilized or reversed after cessation of the drug. There were two deaths in patients treated with the higher dose of fingolimod due to disseminated herpetic infections. Basal cell carcinoma, melanoma, and breast cancer were more common in fingolimod treated patients (19 vs. 7).

Cladribine administration results in the disruption of cellular metabolism, inhibition of DNA synthesis, and subsequent apoptosis of lymphocytes. Cladribine preferentially affects lymphocytes due to their higher ratio of the enzyme deoxycytidine and its resistance to adenosine deaminase. The CLARITY study was a phase III placebo-controlled study of a low (3.5 mg/kg) and high (5.25 mg/kg) dose of oral cladribine for relapsing MS. As compared to placebo, there was a relative reduction in relapse rate of 57.6% and 54.5% for low- and high-dose cladribine, respectively. Both doses of cladribine reduced the risk of sustained disability and effectively decreased inflammatory markers on MRI. The rate of infection in cladribine treated patients was only marginally higher than placebo and most were mild or moderate in severity; notably, 20 infections were cutaneous herpetic zoster. There were three cases of malignant cancer in cladribine treated patients (melanoma, carcinoma of the pancreas and ovary). Similarly, a higher rate of benign cancers occurred in cladribine patients; these included five benign uterine leiomyomas, a choriocarcinoma, and a cervical carcinoma in situ.

■ COMMENTARY

With the completion of the FREEDOMS, TRANSFORMS, and CLARITY studies, the treatment of MS has advanced to include immunosuppressive therapy with distinct advantages over the traditional agents used. Similar to natalizumab, these agents are mechanistically selective, thus decreasing the toxicities which are seen with the older agents. The efficacy of these new agents is apparent; however, their superiority over the IMTs, outside of intramuscular interferon beta-1a, has yet to be ascertained. Although oral therapy is appealing to patients struggling with self-injection, the majority of early MS patients are still likely to be treated with interferon beta or glatiramer acetate until the long-term safety risks of fingolimod and cladribine have been identified. ■

PET-CT Tumor Detection in Patients with Paraneoplastic Syndromes

By Adília Hormigo, MD, PhD

Attending Neurologist, Memorial Sloan-Kettering Cancer Center, and Assistant Professor of Neurology, Weill Medical College of Cornell University

Dr. Hormigo reports no financial relationships relevant to this field of study.

Synopsis: *Colocalized PET-CT is the most sensitive and accurate method for identifying an underlying neoplasm in paraneoplastic neurological syndromes.*

Source: McKeon A, et al. Positron emission tomography - computed tomography in paraneoplastic neurologic disorders. Systematic analysis and review. *ArchNeurol* 2010;67: (doi:10.1001/archneurol.2009.336).

PARANEOPLASTIC NEUROLOGIC SYNDROMES REFER TO symptoms or signs resulting from direct damage to the nervous system remote from the primary site of a neoplasm or any of its metastases. Although these syndromes are rare, they can be the initial presentation of an unknown cancer. Both body computed tomography (CT) and positron emission tomography (PET) scanning have been used for tumor detection.

McKeon and colleagues assess the rate of cancer detection in patients with paraneoplastic neurologic syndromes by using PET-CT. They retrospectively analyzed the data in 56 patients with presumed paraneoplastic neurologic syndromes, whose tumor had not been detected by the conventional work-up including a CT. In 22 patients (39%) PET-CT was suggestive of a cancer and the presence of a neuronal or cytoplasmic paraneoplastic autoantibody in the serum was significantly associated with PET-CT abnormality ($P < 0.001$). The correlation of anatomic localization of CT with metabolic abnormalities in PET led the authors to recommend this test when a paraneoplastic neurologic disorder was suspected.

■ COMMENTARY

The tumor that causes a paraneoplastic neurologic disorder may be too small to be easily detected and often the neurologic disorder appears before the cancer is identified. The work-up for the neurologic syndrome depends on its localization and may include MRI, electrodiagnostic studies, CSF evaluation, and paraneoplastic antibody measurement in the serum. If no tumor is found, the patient should be monitored carefully and studies should be repeated at frequent intervals to look for the appearance of a cancer. Failure to find a cancer does not mean that the disorder is not paraneoplastic.

Previous studies suggested that PET scanning is probably the best screening method and the performance of both PET and CT increases sensitivity. While fluorodeoxyglucose (FDG) PET detects radiolabeled glucose and is a measurement of metabolism, a CT scan gives anatomic information. When you combine the two tests, PET-CT, in a scanner, you obtain the localization of the abnormal metabolic activity. The combination of the two techniques in one scanner increases the yield of tumor detection when compared to the two tests performed separately. ■

Pramipexole + Levodopa in Parkinson's Disease: Is the Whole Greater than the Sum of its Parts?

ABSTRACT & COMMENTARY

By Melissa J. Nirenberg, MD, PhD

Assistant Professor, Neurology and Neuroscience, Weill Cornell Medical College

Dr. Nirenberg reports that she has participated in consulting for Biovail.

Synopsis: *Pramipexole has more than a simple additive benefit in augmenting the motor benefits of levodopa, but also increases the duration and severity of dyskinesias.*

Source: Brodsky MA, et al. Effects of a dopamine agonist on the pharmacodynamics of levodopa in Parkinson disease. *Arch Neurol* 2010;67:27-32.

LEVODOPA AND DOPAMINE AGONISTS (DAS) ARE commonly used treatments for Parkinson's disease (PD). Although DAs tend to have more side effects than levodopa, they are often favored as initial therapy because this strategy delays the onset of motor complications such as wearing off and dyskinesias. Later in the disease, DAs are frequently used as an adjunct to levodopa, to increase "on" times and reduce end-of-dose "wearing-off." While the benefits of combined DA/levodopa therapy are well established, it is unclear whether this is simply an additive benefit, or if there are also pharmacodynamic interactions between these drugs.

The goal of the current study was to examine the effects of pramipexole, a DA, on the motor response to levodopa in PD. The authors used a double-blind, randomized, placebo-controlled, crossover design to evaluate subjects with PD who were experiencing dyskinesias and motor fluctuations as a complication of long-term levodopa therapy. Each of the 13 study subjects was treated with pramipexole (3 mg/day) or placebo for a

four-week period, and then with two-hour intravenous levodopa infusions on each of two consecutive days (after overnight discontinuation of oral levodopa). Blinded neurological assessments were performed concomitant with each levodopa infusion. Subjects were then switched to the other oral agent (placebo or pramipexole) for another four weeks, after which the same levodopa infusions and examinations were repeated. The primary outcome measure was finger-tapping speed, a marker for bradykinesia. Secondary outcome measures included quantitative analyses of dyskinesias and walking speed. All measures were compared at baseline (before levodopa infusion) versus during levodopa infusion, to adjust for the direct benefits of pramipexole on motor function.

Of the 13 study subjects, 10 completed the study and were included in the analysis; three dropped out (two because they were unable to tolerate DA taper during attempted crossover to placebo). Among those 10 subjects, pramipexole with levodopa treatment increased the mean finger-tapping speed beyond the change in baseline, more than doubled the area under the curve for finger-tapping speed, increased the mean peak finger-tapping speed, and improved mean walking speed. In addition, pramipexole prolonged the duration of response after levodopa infusion, and shortened the time to "on." Unfortunately, pramipexole therapy was also associated with increased mean baseline and peak dyskinesia scores. Based on these findings, the authors conclude that pramipexole "augmented the motor response to levodopa beyond a simple additive effect and increased the severity of levodopa-induced dyskinesia."

■ COMMENTARY

Some PD medications—including inhibitors of monoamine oxidase B and catechol-O-methyltransferase—work partially or exclusively by increasing the availability of levodopa / dopamine in the brain. Accordingly, when added to levodopa therapy, these drugs reduce end-of-dose wearing off but can increase dyskinesias and other side effects. In contrast, DAs might potentially work independently of levodopa, through direct stimulation of postsynaptic dopamine receptors. Thus, while DAs are known to boost the clinical effects of levodopa, this may represent a simple additive effect of the two drugs.

In this study, the authors show that pramipexole enhances the motor benefits of levodopa beyond a simple additive effect, suggesting that DAs may affect the pharmacodynamics of levodopa. Study strengths include the randomized, double-blind, placebo-controlled design. Limitations include the small sample size, relatively high dropout rate, and use of intravenous levodopa infusions (since pramipexole may have different pharmacodynamic interactions with intravenous levodopa than with the oral levodopa that is used in clinical practice). All study subjects had PD with motor complications and were recruited from a single academic referral center, such that the findings may not be applicable to other patient populations. ■

Decreased Heart Rate Variability: A Cause for Sudden Unexpected Death in Epilepsy (SUDEP)?

ABSTRACT & COMMENTARY

By Padmaja Kandula, MD

Assistant Professor of Neurology and Neuroscience, Comprehensive Epilepsy Center, Weill Medical College of Cornell University

Dr. Kandula reports no financial relationships relevant to this field of study.

Synopsis: *The authors hypothesize that postictal autonomic dysregulation, as measured by decreased heart rate variability, is a key factor in sudden death in epileptics.*

Sources: Toth V, et al. Periictal heart rate variability analysis suggests long-term postictal autonomic disturbance in epilepsy. *Eur J Neurol* 2010 doi:10.1111/j.1468-1331.2009.02939.x.

DEFINITIVE CRITERIA FOR SUDDEN UNEXPECTED DEATH in epilepsy (SUDEP) exclude death due to trauma, drowning, and status epilepticus. Death can occur with or without evidence of a seizure, can be witnessed or unwitnessed, and occurs without evidence of toxicological or structural abnormality on subsequent postmortem examination. The main risk factor for SUDEP has been poor seizure control, suggesting that in many cases SUDEP is indeed a seizure-related event. Due to the inherent difficulty of formally studying a relatively rare and oftentimes unwitnessed phenomenon, the pathophysiology of SUDEP has not been fully elucidated. The prevailing theory is that seizure-related cardio-respiratory autonomic dysfunction contributes to SUDEP. Heart rate variability indicates the heart's ability to respond to various environmental and physiologic stimuli.

Decreased heart rate variability (HRV) has been postulated as a mechanism involved in autonomic dysfunction leading to SUDEP.

The authors of this study analyzed whether decreased HRV exists in early and late postictal states. Thirty-one patients and 31 seizures (one seizure per patient) were included in this retrospective study after fulfilling criteria for medication-resistant partial epilepsy (failure of greater than two anti-epileptic agents). Nine generalized tonic-clonic seizures (GTCS), 15 complex partial seizures (CPS), and seven simple focal motor seizures were included in the study.

All included patients had a normal baseline EKG and prior evaluation with long-term EEG with synchronized six-lead continuous EKG monitoring. In a blinded fashion, one investigator reviewed seizure onsets and offsets while the second investigator analyzed four separate, 300-second EKG epochs (baseline epoch 30 minutes before seizure onset, preictal epoch five minutes before seizure onset, postictal epoch 10 minutes after seizure offset, late postictal epoch defined as six hours after seizure onset). Measured heart rate variability indices include the following: RRI (mean interbeat interval of normal beats in milliseconds and mean heart rate (HR) on the entire 300-second-long epoch), SDNN (standard deviation of normal-to-normal RRI), coefficient of variation (CV) (SDNN divided by the RR expressed in percent), RMSSD (root mean square of successive RR differences).

To minimize the influence of HR on the HRV, CV was used. The RMSSD index represents the parasympathetic activity found from the analysis of adjacent RR intervals.

The results of the study showed elevation in HR both immediately after seizures and return to baseline six hours postictally. Early postictal HR elevation was higher after GTCS compared to both CPS and simple focal seizures. The authors found a long-lasting, decreased postictal HRV up to six hours after the seizures.

■ COMMENTARY

The HRV describes the oscillations in the interval between consecutive heart beats (RR interval). Over the years, there has been renewed interest in the clinical application of HRV in various disease states. Low HRV has been associated with poor autonomic nervous system adaptation and is an independent predictor of all causes of death.[1]

Although retrospective in design, this study suggests that patients may be at risk for sudden cardiac death not just in the immediate post-ictus phase, but up to six hours later.

This potentially prolonged high-risk period raises a very practical concern in the inpatient hospital setting. Perhaps all epilepsy patients undergoing continuously monitored video EEG studies for characterization of seizures (including anti-epileptic medication wean) be monitored by continuous cardiac telemetry with greater attention to heart rate variability. Although SUDEP likely is caused by the periictal existence of several precipitating factors, this study highlights one potential mechanism of SUDEP and emphasizes the need for further rigorous study of this black-box phenomenon. ■

Reference

1. Dekker JM, et al. Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men. *Am J Epidemiol* 1997;145:899-908.

CME Objectives

Upon completion of this educational activity, participants should be able to:

1. discuss current scientific data regarding the diagnosis and treatment of neurological disease;
2. discuss the pathogenesis and treatment of pain;
3. describe the basic science of brain function;
4. discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
5. identify nonclinical issues of importance for the neurologist. ■

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant. ■

CME Questions

35. The addition of pramipexole to levodopa therapy is likely to do all of the following except:

a. Reduce dyskinesias
b. Reduce bradykinesia
c. Increase walking speed
d. Increase finger tapping speed

36. Which of the following is true about the use of PET-CT in patients with paraneoplastic neurologic syndrome?

a. PET always detects a lesion suggestive of a cancer.
b. Conventional CT is equivalent to PET in revealing the tumor.
c. Detection of a paraneoplastic antibody in serum or CSF is not increasingly associated with PET-CT abnormality.
d. There is a correlation between metabolic abnormality on PET and anatomic changes in CT that may suggest the presence of a cancer.

37. What is the functional mechanism for fingolimod?

a. Stabilization of the blood-brain barrier
b. Monoclonal antibody against α_4-integrin
c. Shifts the proinflammatory TH1 response to anti-inflammatory TH2 response
d. Apoptosis of lymphocytes
e. Functional antagonist of the spingosine-1-phosphate type 1 receptor

38. Significantly increased risk of Guillain-Barré syndrome following vaccination has been reported with which one of the following vaccines?

a. Rabies vaccine
b. Polio vaccine
c. Tetanus toxoid-containing vaccines
d. Quadrivalent conjugated meningococcal vaccine (MCV4)
e. None of the above

39. All of the following statements about SUDEP are true *except*:

a. Drowning, trauma, or status epilepticus are excluded as causes for SUDEP.
b. SUDEP may be caused by drug toxicity.
c. SUDEP is rarely witnessed.
d. SUDEP is associated with poor seizure control.
e. The cause of SUDEP is unknown.

40. All of the following are modifiable risk factors for stroke *except:*

a. Obesity
b. Dietary salt
c. Race / ethnicity
d. Hypertension
e. Diabetes mellitus

Answers: 35. a, 36. d, 37. e, 38. e, 39. b, 40. c

Stroke Alert: A Review of Current Clinical Stroke Literature

By Matthew E. Fink, MD, *Interim Chair and Neurologist-in-Chief, Director, Division of Stroke & Critical Care Neurology, Weill Cornell Medical College and New York Presbyterian Hospital*

Obesity a Major Risk Factor for Stroke that Should Be Modified

Yatsuya H, et. al. Race and sex-specific association of obesity measures with ischemic stroke incidence in the Atherosclerosis Risk in Communities (ARIC) study. *Stroke* 2010; DOI: 10.1161/STROKE.109.566299

IN THIS PROSPECTIVE, POPULATION-BASED STUDY OF 13,549 middle-age black and white men and women in four U.S. communities, who, at the time of enrollment were free of cancer and cardiovascular disease, the investigators showed that abdominal obesity raised the risk of stroke in all groups, men and women, white and black.

The thinnest white women suffered about 1.2 strokes per 1,000 person-years, while their black counterparts suffered 4.3 strokes per 1,000 person-years. Obese black men had the highest incidence of stroke — 8.0 per 1,000 person-years. In all comparative groups, obese black men and women had between two and three times the stroke risk of their white counterparts. Correction for hypertension and diabetes attenuated the effect of obesity, but both of these conditions are strongly associated with obesity. Although there is no proof from any randomized clinical trials, we believe that aggressive weight reduction should be part of any stroke risk reduction program. But, it will take decades to prove this hypothesis.

Aspirin Alone or Aspirin Plus Extended-release Dipyridamole Is Equally Effective as Early Treatment for Transient Ischaemic Attack or Stroke

Dengler R, et al. Early treatment with aspirin plus extended-release dipyridamole for transient ischaemic attack or

ischemic stroke within 24 h of symptom onset (EARLY trial): a randomized, open-label, blinded-endpoint trial. *Lancet Neurol* 2010;9:159-166.

TREATMENT GUIDELINES RECOMMEND ANTIPLATELET therapy for patients with non-cardioembolic stroke or TIA (aspirin 50–325 mg, aspirin plus extended-release dipryridamole, or clopidogrel). For long-term secondary prevention of stroke, aspirin plus extended-release dipyridamole (ASA-DPM) has been shown to be more effective than aspirin monotherapy, and clopidogrel is more effective in reducing combined vascular events and death. Based on the PRoFESS trial, there is no difference between clopidogrel and ASA-DPM in stroke recurrence.

However, the best antiplatelet treatment in the acute setting of stroke and TIA is unknown because the secondary prevention trials enrolled patients anywhere from one month to six months after symptom onset. The EARLY trial was designed to answer this question by enrolling 543 patients within 24 hours of symptom onset. Half received 100 mg of aspirin daily for the first seven days; the other half received ASA-DPM for the first seven days, and then all of the patients were treated with ASA-DPM until follow-up at 90 days. The primary end point was the modified Rankin scale score, and there was no significant difference between the groups at 90 days. A composite secondary outcome that looked at adverse events (non-fatal stroke, TIA, non-fatal myocardial infarction, major bleeding, and mortality) also showed no significant differences between the groups at 90 days. There was a higher dropout rate in the early ASA-DPM group due to headache.

Reducing Salt Intake Will Reduce the Risk of Stroke and Death

Bibbins-Domingo K, et al. Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med* 2010; Jan 20 [Epub ahead of print].

THE U.S. DIET IS HIGH IN SALT, MOSTLY FROM PROCESSED foods. Men consume more than 10 gm of salt per day and women more than 7 gm per day, far in excess of the recommendations of the Department of Health and Human Services. Hypertension remains a major public health challenge, with less than 50% of those affected getting optimal treatment, and the age-adjusted incidence of hypertension is rising.

In this setting, the investigators created a model for determining the health benefits of a population-wide reduction in dietary salt by 3 gm per day — a realistic and achievable level. A successful effort to reduce dietary salt could reduce new cases of stroke by 32,000 to 66,000 and reduce annual deaths from any cause by 44,000 to 92,000. The entire population would benefit, with blacks receiving a greater benefit than whites, and women having a greater reduction in stroke compared to men. Health care costs could be reduced by $10 billion to $24 billion, and dietary salt reduction would be more cost-effective than using blood pressure medications to lower blood pressure for everyone who has hypertension.

Proteinuria Associated with Cerebral Microbleeds, and May Predict Future Risk for Intracerebral Hemorrhage

Ovbiagele B, et al. Strong independent correlation of proteinuria with cerebral microbleeds in patients with stroke and transient ischemic attack. *Arch Neurol* 2010;67:45-50.

FROM AN OBSERVATION NEVER BEFORE ANALYZED, THE investigators correlated the degree of proteinuria with the presence and number of cerebral microbleeds (CMB), as measured on gradient-echo T2-weighted MRI, in an unselected group of patients with ischemic stroke and TIA. Of 236 patients (mean age, 70 years; 53% female), 31% had CMB and 38% had proteinuria. In a multivariable analysis with presence of CMB as the outcome, the following associations were found — higher urinary protein (OR = 2.33), being female (OR = 2.2.9), atrial fibrillation (OR = 2.49), elevated homocysteine (OR = 1.1.9), small-vessel disease subtype (OR = 2.95). All were associated with a higher number of CMB.

The authors speculate that the association of CMB and proteinuria may indicate a widespread endothelial dysfunction that results in blood vessel fragility and leakage of protein, as well as small bleeds from small cerebral arteries. We have no way to know how many of these patients might have cerebral amyloid angiopathy and whether proteinuria is associated with that disorder. Regarding treatment, the authors stress the importance of good blood pressure control to help the brain as well as the kidneys.

In Future Issues:

Vasculitis and Neuropathy

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Helping HF patients feel better with iron

Source: Anker SD, et al. *N Engl J Med* 2009;361:2436-2448.

GLOBALLY DEFINED, HEART FAILURE exists when delivery of oxygen to the tissues is insufficient to meet demand. Anything that compromises oxygen delivery or impairs blood oxygenation can only compound the situation. Accordingly, patients with chronic heart failure (CHF) who are anemic might understandably suffer greater symptom burden or limitations as a result.

Anker et al enrolled patients with CHF (n = 459) and iron deficiency as documented by a low ferritin level. Patients were randomized to receive either placebo or iron intravenously (as ferric carboxymaltose) and followed for 6 months. The primary outcomes of the trial were self-reported global assessment and NYHA functional class.

Iron was administered as a 4 mL bolus IV (200 mg iron) weekly until iron levels were restored (as measured by ferritin, hemoglobin, and transferrin saturation), and then monthly until the end of the trial.

At the end of the trial, both the global assessment and NYHA class were improved to a statistically significant degree more in the iron group than by placebo. There were no serious adverse reactions with the ferric carboxymaltose.

Previous smaller studies have generally had similarly favorable outcomes. Interestingly, both this trial and earlier trials have found that iron supplementation benefits CHF patients with or without anemia, suggesting that more study of the pathophysiologic role of iron in CHF is needed. ■

COPD and osteoporosis

Source: Ferguson GT, et al. *Chest* 2009;136:1456-1465.

OF THE TOP 10 CAUSES OF DEATH IN America, COPD (fourth) might be likened to the Rodney Dangerfield of mortal maladies: "It don't get no respect." Our pulmonology colleagues like to remind us that in contrast to the other 9 top 10 mortal disorders — which are either improving or at least leveling off — COPD mortality is actually rising. One way to awaken clinicians' interest in COPD is to remind them that it's not just about the lungs: Patients with COPD suffer detriment in multiple tissue compartments, such as bone health.

The TORCH trial (Towards a Revolution in COPD Health) studied inhaled fluticasone, inhaled salmeterol, both, or placebo in more than 6000 subjects. A subgroup study (n = 658) looked at the effects on BMD in each treatment arm.

At baseline, more than half of both men and women with COPD had either osteoporosis or osteopenia. Although frank osteoporosis was more common in women (30% vs 18%), osteopenia was equal. This is a critically important observation, since most fractures happen in subjects with osteopenia not osteoporosis. (This is likened to the situation in hypertension: Even though the risk of severe HTN is greater, since there are so many more folks with stage 1 or stage 2 hypertension, most of the CV burden of HTN is not shouldered by folks with severe HTN).

The good news: There was no meaningful change in BMD related to inhaled steroids (alone or in combination with salmeterol). The bad news: Osteopenia and osteoporosis are frighteningly commonplace in COPD. ■

Secondary prevention of depression: Cognitive therapy

Source: Bockting CL, et al. *J Clin Psychiatry* 2009;70:1621-1628.

FOR MILD-TO-MODERATE DEPRESSION, the literature indicates that cognitive therapy (COG) and pharmacotherapy have similar beneficial effects, although pharmacotherapy is often less expensive and may provide symptomatic improvement more quickly. Because depression is recurrent, it is important to identify whether long-term cognitive therapy is helpful to prevent such recurrences.

To investigate this issue, Bockting et al enrolled major depressive disorder patients who had achieved remission (n = 172) and compared usual care with usual care plus COG. The COG was administered as weekly 2-hour group sessions over a 2-month period. After this 2-month COG intervention, both groups were followed for 5.5 years.

The group that had received 8 weeks of COG had a 21% relative risk reduction for recurrence over the next 5 years. Suicide (60% of cases are related to depression) remains in the top 10 causes of death. The value of COG treatment for even as brief a period as 8 weeks

might have substantial long-term clinical payoff. ■

Prediabetes treatment: A wealth of opportunity

Source: Rhee MK, et al. *Diabetes Care* 2010;33:49-54.

It is estimated that almost 40 million Americans have diabetes, and more than twice that many have prediabetes. Clinical trials from the United States and various other nations indicate that prediabetes progresses at a rate of 6%-10% each year to frank diabetes. Fortunately, the menu of interventions that forestall development of diabetes from prediabetes continues to expand. It now includes diet, exercise, metformin, thiazolidinediones, acarbose, and orlistat.

In the recent past, it has been suggested that persons with prediabetes merit pharmacotherapy with metformin (in addition to lifestyle) if they have both impaired fasting glucose and impaired glucose tolerance, and any one of: age > 60 years, BMI > 30 kg/m^2, family history of diabetes, elevated triglycerides, reduced HDL, hypertension, or A1c > 6%.

Rhee et al invited employees of the Grady Health System, Emory HealthCare and University, and Morehouse School of Medicine to be screened for diabetes. Of the volunteers who qualified for glucose tolerance testing (n = 1581), the combination of factors sufficient to merit metformin treatment was 8.1%; an additional 4.6% of subjects were newly diagnosed as frankly diabetic. Now that firm indications for pharmacotherapy of prediabetes are established, clinicians have a wealth of opportunity for timely intervention. ■

Aspirin for primary prevention in diabetes? Maybe

Source: Calvin AD, et al. *Diabetes Care* 2009;32:2300-2306.

The syllogism seemed so simple: 1) The CV risk reduction of aspirin (ASA) in primary prevention is linearly related to baseline risk; 2) DM is a high-risk population for CV events; and 3) therefore, ASA should be really good for primary prevention in diabetics. Well, it's not quite so simple.

The authors of this report in *Diabetes Care* performed a random-effects meta-analysis and Bayesian logistic regression (whatever that means, you ask?) to provide an opinion about whether aspirin is beneficial for primary prevention in diabetes. Their conclusion, based upon 8 trials that included patients with diabetic subgroups among the overall cohort (5 trials) as well diabetes-only trials (3 trials), is that the benefits of aspirin are similar in persons with or without diabetes.

I don't really know what "a random-effects meta-analysis and Bayesian logistic regression" means, but it would appear encouraging that this analysis, which incorporates data from 8 major clinical trials totaling more than 90,000 study subjects suggests, that aspirin might be a good thing.

Trouble is, I'm just not so sure. First, it is a matter of debate whether there is really any such thing as primary prevention in diabetes; after all, adult type 2 diabetics are considered a CV risk equivalent, since their CV risk (without ever having an MI) is as great as a person who has already had one. So, is aspirin in a diabetic primary or secondary prevention?

Secondly, the only 2 recent trials that studied only diabetics and were primarily designed to study the effects of aspirin in diabetics (the JPAD and POPADAD trials) both failed to find a beneficial effect of aspirin.

For the time being, popular opinion suggests that aspirin is a good thing. I'm not so sure. ■

Dementia: No simple answer

Source: Snitz be, et al. *JAMA* 2009;302: 2663-2670.

The burgeoning population of advanced seniors (age > 75 years) includes an ever-growing population of persons with cognitive impairment and dementia. Popular complementary and alternative interventions to forestall dementia abound, among which it has been suggested that ginkgo has memory-preserving qualities.

Unfortunately, the data supporting long-term favorable outcomes for cognitive function are lacking. Nonetheless, because *Ginkgo biloba* has a popular impression of being favorable for mental faculties, and because earlier trials have faced limitations of trial duration, size, and population age, more conclusive insights have been sought.

A study sample of community-dwelling seniors (n = 3069; mean age, 79 years) was administered either 120 mg of ginkgo or placebo twice daily for a median follow-up of 6.1 years. Rates of decline in cognitive function, and numerous other metrics including attention, language, executive function, and others, were not statistically improved by administration of ginkgo. Although there were no significant adverse effects attributable to ginkgo, there is no sound basis on which to advocate for long-term cognitive effects from ginkgo. ■

Correction

In the January brief entitled "The relationship of FPG and A1c to diabetic retinopathy" (page 1), the recommended A1c threshold for the diagnosis of diabetes should have read 6.5% instead of 6.2%. ■

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Oral Treatments for Relapsing-remitting MS

In this issue: Two oral medications for relapsing-remitting MS in phase III development; antihypertensives find new uses; *Ginkgo biloba* does not prevent cognitive decline in elderly; and FDA Actions.

Oral medications for relapsing-remitting MS

Two new oral medications are effective treatments for relapsing-remitting multiple sclerosis (MS) according to three studies published on-line in the *New England Journal of Medicine*. Fingolimod and cladribine differ in the mechanism of action but both reduce the number of potentially auto-aggressive lymphocytes that are available to enter the central nervous system. In the Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) trial, two different doses of cladribine were compared to placebo with the endpoint being relapse at 96 weeks. Both doses were more effective than placebo at preventing relapses and reducing brain lesion count on MRI ($P < 0.001$ for all comparisons). The drug was associated with lymphocytopenia and a higher risk of herpes zoster.

Fingolimod was compared to placebo in the FREEDOMS trial and compared to injectable interferon in the TRANSFORMS trial. The 24-month FREEDOMS trial compared two doses of fingolimod to placebo and similarly found a lower rate of relapse ($P < 0.001$ for both doses) and disability progression ($P = 0.02$ for both doses). The drug also reduced the number of new lesions found on MRI. Significant side effects included bradycardia, AV block, macular edema, elevated LFTs, and mild hypertension. When compared to interferon, fingolimod was associated with significantly lower annualized relapse rates at both doses tested ($P < 0.001$ for both comparisons), although there was no significant difference with respect to progression of disability. Two fatal infections occurred with the higher dose of fingolimod (disseminated primary varicella zoster and herpes simplex encephalitis). (All three studies published on-line at www.NEJM.org, Jan. 20, 2010).

An accompanying editorial calls the arrival of oral formulations of MS drugs "welcome news for the estimated 2.5 million people worldwide with this chronic, disabling disease." While suggesting these drugs "support a change in treatment approach to directly prevent immune-related injury," the editorial also suggests that long-term goals of MS therapy are currently lacking (published online at www.NEJM.org, Jan. 20, 2010). Both drugs are in phase III trials for treatment of MS; cladribine is currently approved in parenteral form for treatment of hairy cell leukemia. ■

Antihypertension drugs for AF and dementia?

Different classes of blood pressure (BP) medications may have different benefits according to two new studies. In the first study, researchers from the United Kingdom performed a nested

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case-control analysis to evaluate whether different antihypertensive drug classes may alter the risk for atrial fibrillation. The researchers reviewed records from a large patient population, specifically patients who were on a single agent for lowering BP. A lower odds ratio (OR) for atrial fibrillation was noted with ACE inhibitors (OR, 0.75; 95% confidence interval [CI], 0.65-0.87), angiotensin receptor blockers (ARBs) (OR, 0.71; 95% CI, 0.57-0.89), and beta-blockers (OR, 0.78; 95% CI, 0.67-0.92) compared with current exclusive therapy with calcium channel blockers. Although the researchers were unable to assess why patients were receiving one class of blood pressure medicine over another, they concluded that long-term therapy with ACE inhibitors, ARBs, or beta-blockers reduces the risk for atrial fibrillation compared with calcium channel blockers. These findings generally relate to patients with mild hypertension, since patients on multiple drugs were excluded from the study (*Ann Intern Med* 2010;152:78-84).

In the second study, researchers from Boston set out to investigate whether ARBs reduce the risk of Alzheimer's disease and dementia or reduce the progression of both diseases. More than 800,000 predominately male participants, age 65 or older with cardiovascular disease, were studied. Patients were divided into three cohorts (ARBs, lisinopril, and other cardiovascular drugs as a comparator) and followed over 4 years, with adjustments for age, diabetes, stroke, and cardiovascular disease. Hazard rates for dementia in the ARB group were 0.76 (95% CI, 0.69-0.84) compared to the cardiovascular comparator, and 0.81 (95% CI, 0.73-0.90) compared to the lisinopril group. In patients with pre-existing Alzheimer's disease, ARBs were associated with significantly lower risk of admission to a nursing home. The combination of the ARB and ACE inhibitor was better than ACE inhibitor alone in preventing dementia and reducing admission to nursing home. The authors conclude that ARBs are associated with a significant reduction in the incidence and progression of Alzheimer's disease and dementia compared to ACE inhibitors or other cardiovascular drugs (BMJ 2010;340:b5465, doi: 10.1136/bmj.b5465, published on-line Jan. 12, 2010). An accompanying editorial points out that several studies have shown that treatment with any antihypertensive is associated with a lower risk of cognitive decline or incident dementia in older adults. What is not clear is whether some antihypertensives also have other biological mechanisms that help prevent dementia. It is plausible that ARBs are more neuroprotective than other drugs because of their effect on type 2 angiotensin receptors in the brain (*BMJ* 2010:340;b5409, doi: 10.1136/bmj.b5409, published on-line Jan. 12, 2010). ■

Ginkgo does not prevent cognitive decline

The National Center for Complementary and Alternative Medicine (NCCAM) was founded during the Clinton administration as part of the National Institutes of Health to investigate complementary and alternative medicines. Many of the NCCAM-funded studies, however, have shown no benefit from complementary or alternative treatments, and that is the case with a new study looking at *Ginkgo biloba* and cognitive function in older adults. *Ginkgo biloba*, which is widely marketed as an aid to preventing cognitive decline and dementia, was previously found to have no benefit in reducing the incidence of Alzheimer's disease or dementia overall (*JAMA* 2008;300:2253-2262).

In a new study sponsored by NCCAM, researchers set out to determine whether *Ginkgo biloba* slows the rate of global or domain-specific cognitive decline in older adults. More than 3000 participants age 72-96 years were enrolled and randomized to *G. biloba* 120 mg or placebo twice daily. Rates of change over time in two different objectives cognitive tests, as well as neuropsychological tests, were the primary endpoints. There was no difference in the decline in cognitive scores between *Ginkgo biloba* and placebo in any of the domains including memory, attention, and visuospatial abilities, language, or executive functions. There was also no difference in the rate of change in the standardized cognitive exams. The authors conclude that compared to placebo, *Ginkgo biloba* did not result in less cognitive decline in older adults (*JAMA* 2009;302: 2663-2670). ■

FDA Actions

Novo Nordisk has received approval to market liraglutide, a once-daily injection for the treatment of type 2 diabetes in adults. The drug is a glucagon-like peptide-1 receptor agonist similar to exanatide (Byetta®). The company is required to perform additional post-marketing cardiovascular studies as well as a 5-year epidemiological study to evaluate the risk of thyroid cancer. Liraglutide will be marketed under the trade name Victoza®. ■