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INSIDE



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# Cognitive Dysfunction and Depression in Retired NFL Players

Abstract and commentary

***By Nitin K. Sethi, MD***

*Assistant Professor of Neurology, Weill Cornell Medical College*

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

***Synopsis:*** *In former, aging, National Football League players, fluid-attenuated inversion recovery scans showed increased total and deep white matter hyperintensity volumes, while diffusion tensor imaging showed decreased fractional anisotropy reflecting white matter disruption, and this is associated with cognitive impairments and depression.*

**Source:** Hart J Jr, et al. Neuroimaging of cognitive dysfunction and depression in aging retired National Football League players: A cross-sectional study. *JAMA Neurol* 2013;70:326-335.

THE PERILS OF MULTIPLE CONCUSSIONS SUSTAINED DURING CONTACT SPORTS — such as boxing, mixed martial arts, American football, and ice hockey — are increasingly being recognized. Recent medical evidence links multiple concussions sustained during contact sports to later life development of cognitive impairment and behavioral and mood changes in athletes. Recent suicides among former National Football League (NFL) players and postmortem diagnosis of chronic traumatic encephalopathy (CTE) in athletes with a history of multiple concussions has generated a flurry of research to identify neuropsychiatric and neuroimaging correlates of repeated concussions and CTE.

Hart and colleagues investigated the frequency of cognitive impairment and depression in aging former NFL players using neurocognitive tests, clinical neurological assessments, and neuroimaging protocols including fluid-attenuated inversion recovery (FLAIR) MRI, diffusion tensor imaging (DTI), hemosiderin scanning, and arterial spin labeling (ASL). They examined 34 retired players, ages 41 to 79 (mean age = 61.8). Twenty-six of 34 underwent detailed neuroimaging studies (eight players had severe claustrophobia and were unable to tolerate imaging) and were compared

with an age, sex, and educationally matched normal group. Cognitive deficits in naming, word finding, episodic memory (verbal and visual), and depression were found to be more common in aging former NFL players who reported a history of multiple concussions compared to matched healthy controls with no history of concussion. FLAIR scans showed increased total and deep white matter hyperintensity volumes while DTI scans showed decreased fractional anisotropy, reflecting white matter disruption in former NFL players who reported multiple concussions during their athletic careers. ASL studies were variable, with some players showing increased blood flow in frontal and cingulate areas, and others showing decreased blood flow. The authors recommend future studies of larger samples of professional athletes with multimodal neurobehavioral and neuroimaging studies and correlation with autopsy findings to confirm these preliminary results.

**■ COMMENTARY**

Signs of early CTE have been identified in the brains of former NFL players at autopsy. An association between repeated concussions and mild cognitive impairment has been suggested.[1,2] Whether multiple concussions may also lead to amyotrophic lateral sclerosis is an ongoing debate. At present, CTE can only be conclusively diagnosed by postmortem examination of the brain. There is an urgent need for distinct neuroimaging and neurocognitive biomarkers to help identify the disease process during its early stages of evolution so that both professional and amateur athletes can be protected from the devastating consequences of chronic traumatic brain injury.[3] The Hart study identifies MRI biomarkers that measure white matter disruption and further strengthens the evidence for structural and functional dysfunction in the cortical and subcortical pathways, suggesting that a dynamic process may underlie the cognitive and neuropsychiatric dysfunction in aging retired NFL players who sustained multiple concussions during their professional football careers. ■

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Please call **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.


# Should We Use Combination Therapy for Multiple Sclerosis?

Abstract & commentary


***By Susan Gauthier, DO, MS***

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*Dr. Gauthier reports she receives research support from EMD Serono, Biogen Idec, and Novartis Pharmaceuticals, and is on the speakers bureau for Biogen Idec and Teva Neurosciences.*


***Synopsis:*** *The combination of interferon beta 1a (30 mcg IM weekly) and glatiramer acetate was not more effective on annualized relapse rate in multiple sclerosis compared to either treatment alone.*


**Source:** Lublin F, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Ann Neurol* 2013;73:327-340.

There are multiple FDA-approved treatments for multiple sclerosis (MS), but the injectables, interferon beta (both 1a and 1b) and glatiramer acetate (GA), have been available for more than a decade. The injectables are known to be partially effective and patient compliance remains difficult. Therefore, several new oral agents have arrived on the market with varying levels of effectiveness and safety. Injection therapy with interferon or GA for MS continues to have the most favorable short- and long-term safety profiles; thus, an attempt to improve efficacy through a combination of these medications was of great interest and was the driving force behind the recently pub-

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lished CombiRx study. Given that both interferon beta 1a (IFN) and GA are likely to have different mechanisms of action, there was an expected benefit from the combination over and above each of these drugs used as monotherapy.

The CombiRx study was a three-arm, randomized, double-blind, placebo-controlled study with a 2:1:1 randomization of the combination of IFN+GA or each individual agent with matching placebo. Participants were in the core study for a minimum of 3 years and up to 7 years in an extension phase. Inclusion criteria required two relapses within the past 3 years, and a new lesion on MRI could qualify for a relapse. The primary outcome was annualized relapse rate (ARR). Secondary outcome measures included progression on clinical disability scores (EDSS, MSFC) and a composite MRI score (gad+, T2, T1 lesions, and atrophy measure). The study was powered to compare the combination of IFN+GA to the better of the two monotherapy groups, and the sample size allowed for a comparative efficacy analysis between IFN and GA. The superior of the two monotherapies was GA (0.16 vs 0.11, $P = 0.022$); however, the combination of IFN+GA was not superior to GA ($P = 0.27$) alone. There were no differences between any of the groups on clinical progression (EDSS or MSFC) or on the composite MRI score. Differences in individual lesion counts were noted among the groups, wherein the combination of IFN+GA was superior to the nominal winner, IFN, in reducing the number of enhancing lesions ($P = 0.01$) and combined unique lesion activity (CUA, the sum of new enhanced, unenhanced, and enlarged lesion, $P < 0.0001$) over the course of 3 years. The effect on brain atrophy was similar among all three groups, and, interestingly, the pattern of tissue loss was very similar among all treatment arms with the majority occurring in the first year (average of all subjects 2.7%), followed by 0.7% in year 2 and 0.01% in last year. Disease activity-free status (DAFS) — which is defined as no relapses, no EDSS progression, and no new CUA — did not differ among the two monotherapy treatment arms; however, the combination of IFN+GA was superior to both (GA: $P < 0.0001$, IFN: $P = 0.0004$). There were no safety issues identified during the study.

**■ COMMENTARY**

Unfortunately, the combination of IFN+GA did not show superiority on ARR but did show a benefit on overall DAFS. The use of DAFS as an outcome measure in clinical trials (or as a goal for standard of care treatment) is controversial within the field, given its dependence on MRI. However, given the low ARR in this and other modern clinical trials, which has yet to be fully understood, the role of the MRI as a sensitive marker of continued disease activity might need to be reconsidered. The state of true remission, based on imaging modalities, is accepted within many other disease fields, but in the field of MS, a tolerance for MRI disease activity still exists. This tolerance is due, in part, from the lack of a cross-sectional relationship between lesions and disability, the so-called clinical-MRI paradox of MS, and because the safety profiles of the more efficacious drugs are complicated. Since combination therapy failed to show superiority on the standard clinical measures, it is difficult to conceive of this moving into our current treatment algorithm. Of great importance, this study highlighted an overall low ARR and clinical progression rates as well as very low measures of atrophy (within second and third year) among patients treated with IFN and GA monotherapy, suggesting that many patients can receive an effective clinical and potentially neuroprotective benefit from these drugs. Therefore, considering the favorable long-term safety profile of injectable therapy, these treatments remain strong viable options. ■

# Are There Interactions Between Vascular Brain Disease, Amyloid Deposition, and Dementia?

Abstract & commentary

***By Michael Lin, MD, PhD***

*Assistant Professor of Neurology and Neurosciences, Weill Cornell Medical College*

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

***Synopsis:*** *In a study of the elderly who are normal or have mild cognitive impairment, vascular brain disease*

# Stroke Alert: A Review of Current Clinical Stroke Literature

***By Matthew E. Fink, MD,*** *Professor and Chairman, Department of Neurology, Weill Cornell Medical College, and Neurologist-in-Chief, New York Presbyterian Hospital*

## Which Patients Taking Warfarin for Atrial Fibrillation Have an Ongoing Risk for Stroke?

**Source:** Albertson IE, et al. Risk of stroke or systemic embolism in atrial fibrillation patients treated with warfarin. A systematic review and meta-analysis. *Stroke* 2013;44:1329-1336.

In a review of six randomized clinical trials, with a total of 58,883 patients treated with warfarin for atrial fibrillation, the authors calculated the risk of ongoing embolic stroke and used regression analysis to determine the characteristics that were associated with increased stroke risk. They found the following significant risk factors for stroke in those who were taking oral anticoagulants, with a 95% confidence interval — age > 75 years (relative risk [RR] = 1.46), female sex (RR = 1.30), previous stroke or TIA (RR = 1.85), moderate and severe renal impairment (moderate RR = 1.54 and severe RR = 2.22), previous aspirin use (RR = 1.19), Asian race (RR = 1.70), and CHADS score ≥ 3 (RR = 1.64).

These risk factors should be assessed and monitored in all patients who are taking warfarin in order to lower their stroke risk as much as possible. It is not known whether the new direct thrombin inhibitors and factor X inhibitors will demonstrate similar findings as those of patients who are taking warfarin. ■

## Who Gets Chronic Pain After a Stroke?

**Source:** O'Donnell MJ, et al. Chronic pain syndromes after ischemic stroke. PRoFESS Trial. *Stroke* 2013;44:1238-1243.

The frequency and consequences of chronic pain syndromes after stroke are poorly understood. The authors used prospective data from the Prevention Regimen for Effectively Avoiding Second Stroke (PRoFESS). Patients were followed for up to 2.5 years, and included 15,754 patients with all types of ischemic stroke. On the last follow-up visit, a structured pain questionnaire was administered to identify those who developed a chronic pain syndrome, and 1665 participants (10.6%)

*and brain amyloid deposition appear to be independent risks for dementia.*

**Source:** Marchant NL, et al. The aging brain and cognition. Contribution of vascular injury and a-beta to mild cognitive dysfunction *JAMA Neurol* 2013;70:488-495.

Alzheimer's disease (AD) and vascular brain injury (VBI) are the leading causes of dementia in aging, with AD considered to be the most common cause. However, AD and VBI frequently co-occur, and vascular risk factors are also risk factors for AD. To assess the relationship between AD and VBI, Marchant and colleagues used amyloid (Pittsburgh B, PiB) PET to assess the burden of amyloid deposition and MRI to assess the burden of VBI (infarcts and white matter disease). Findings were correlated with performance on a cognitive test battery. There were 30 subjects with normal cognition (mean age = 77.1), 24 subjects with mild cognitive impairment (mean age = 78), and seven subjects with mild dementia (mean age = 79.8).

Overall, 56% of subjects had at least one infarct on MRI, and 48% were PiB-positive. VBI and amyloid were independent factors; the presence of an infarct did not increase the likelihood of PiB-positivity, and there was no relationship between white matter hyperintensity and global PiB index. In multivariate regressions, including demographic variables and measures of VBI and amyloid, infarction in cortical and deep gray matter was associated with decreased performance on tests of verbal memory and executive functioning. In contrast, neither amyloid nor white matter hyperintensity were significant predictors of cognition.

These data suggest a more prominent role for vascular disease in cognitive decline with aging. Other recent literature also points in the same direction. For example, Westover et al showed that finding even one microinfarct on routine neuropathologic examination suggests the presence of hundreds of microinfarcts throughout the rest of the brain.[1]

**■ COMMENTARY**

The lack of correlation between amyloid PET imaging and cognition is not surprising. It has been known for some time that plaque is not the best pathologic correlate of cognitive decline in AD. Amyloid is thought to be an

were found to have chronic pain. The etiologies were central poststroke pain (2.7%), peripheral neuropathic pain (1.5%), pain from spasticity (1.3%), and pain from shoulder subluxation (0.9%). More than one pain subtype was reported in 86 participants (0.6%).

In an analysis of risk factors for the development of pain, the following predictors were significant — stroke severity, female sex, alcohol intake, statin use, depressive symptoms, diabetes mellitus, antithrombotic medications, and peripheral vascular disease. Patients who developed a chronic pain syndrome were also more likely to become dependent (OR = 2.16; 95% CI 1.82-2.56). In addition, patients who had chronic pain as a result of peripheral neuropathy, spasticity, or shoulder subluxation were more likely to have cognitive decline. Chronic pain syndromes occur in about 10% of stroke patients and may have significant impact on recovery and functional outcomes. ■

## Clinical Features and Outcome of Basilar Artery Occlusion

**Source:** Ohe Y, et al. Clinical review of 28 patients with basilar artery occlusion. *J Stroke Cerebrovasc Dis* 2013;22:358-363.

The authors performed a retrospective review of clinical presentation, treatment, and outcomes in 28 patients with basilar artery occlusion. Ages ranged from 39 to 100 years, with a mean age of 72. There were 18 men and 10 women. Hypertension was present in 21 patients, diabetes in 4, dyslipidemia in 11, and atrial fibrillation in 10 patients. Clinical severity, based on a high NIHSS score and a low Glasgow Coma Score, predicted a poor outcome with 79% of the patients having a poor outcome, and only 21% recovering with a good outcome. MRI showed the location of the infarcts to be in the caudal pons in 6 patients, mid-pons in 9, and upper pons and midbrain in 13 (top of the basilar). There were associated infarcts in the cerebellum, thalamus, and occipital lobes in most patients. One patient was treated with IV thrombolysis, and five patients underwent percutaneous endovascular angioplasty, with three successfully recanalized. However, two of the three who were recanalized still had poor neurological outcomes.

There were no underlying risk factors that predicted a good outcome compared to a bad outcome. The clinical severity on admission predicted outcome, and the various therapies did not appear to influence the outcomes, although the number of patients is too small to draw any firm conclusions. ■

early, initiating event in AD pathogenesis, and more downstream events, such as tangle formation or synapse loss, correlate better with loss of cognition. Thus, studies focused on amyloid may underestimate the contribution of AD pathology to dementia.

Nonetheless, this paper emphasizes the importance of vascular disease in cognitive health. Since vascular risk factors are treatable, this may be the most important intervention to reduce the risk of dementia in the population. Moreover, even in subjects with AD, treatment of vascular risk factors is associated with slower cognitive decline.[2] Counseling on vascular risk factors should be a standard part of every memory disorders clinic visit. ■

### References


1. Westover mb, et al. e stimating cerebral microinfarct burden from autopsy samples. *Neurology* 2013;80:1365-1369.
2. d eschaintre y, et al. t reatment of vascular risk factors is associated with slower decline in Alzheimer disease. *Neurology* 2009;73:674-680.


# Acute Seizures and Epilepsy Risk in Pediatric Intracerebral Hemorrhage

Abstract & commentary


***By Sotirios Keros, MD, PhD***

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


***Synopsis:*** *Children with intracerebral hemorrhage are at increased risk for seizures and epilepsy compared to adults, particularly those who develop elevated intracranial pressures.*

**Source:** Beslow LA, et al. Pediatric intracerebral hemorrhage: Acute symptomatic seizures and epilepsy. *JAMA Neurol* 2013;70:448-454.

Spontaneous intracranial hemorrhage (ICH) is a known risk factor for acute seizures as well as the subsequent development of epilepsy. The association between seizures and ICH appears to be particularly strong in children and neonates relative to adults. The existing pediatric data are somewhat limited, however, by reliance on small sample sizes, retrospective studies, non-uniform definitions, and unclear or unspecified follow-up durations.

The present study by Beslow et al describes data obtained prospectively from both neonates (> 37 weeks gestational age and < 28 days old) and children (28 days to 18 years) who presented with ICH from three institutions over a 5-year period. There were 87 eligible subjects, of which 73 were enrolled into the study. Of the 20 neonates, 70% had intraparenchymal hemorrhage (IPH) with extension into the ventricles (IVH), while 15% each had isolated IPH or IVH. Of 53 children, 55% had IPH, 11% IVH, and 34% with both IPH and IVH. The etiology of ICH in neonates was not found in 60% of cases, while 25% had an underlying coagulopathy, 10% had a cavernous malformation, and 5% had an arteriovenous malformation. In contrast, only 17% of children had an unknown etiology for ICH, with 50% of children found to have either an arteriovenous or cavernous malformation, and roughly 10% each diagnosed with an aneurysm, coagulopathy, or were on anticoagulants. There was one child (2%) with moyamoya and one child with a developmental venous anomaly.

The study divided the temporal occurrence of seizures into three categories: seizures at presentation, acute seizures (after presentation but within 7 days of ICH), and remote seizures > 7 days from presentation. The decision to obtain either a routine EEG or continuous EEG monitoring was determined by the treating physician, as was the initiation and choice of any antiepileptic drugs. For analysis, seizures included either clinically evident seizures or electrographic seizures. In the neonatal group, 60% had seizures as at least one of their presenting symptoms, compared with only 36% in children ($P$ = 0.07). Of the neonates presenting with seizures, 83% were defined as being in status epilepticus (seizures lasting > 30 minutes) compared to 26% in children. Neither cortical location of the ICH nor the presence of a vascular malformation predicted risk of seizure at presentation. Seven children (13%) had a seizure in the acute period. None of the neonates had seizures in the first 7 days after presentation.

Of 67 surviving subjects, there was a trend toward children being more likely to have a remote seizure compared to neonates (24% vs 12% with $P$ = 0.05, but $P$ increased to 0.27 after a correction for multiple comparisons). Children also tended to be at increased risk to develop epilepsy (16% vs 6%, $P$ = 0.04, but 0.20 after correction), defined as two or more unprovoked remote symptomatic seizures during follow-up, with the median duration of follow-up approximately 1 year for each group.

Twenty-six of the surviving subjects had elevations in intracranial pressure (ICP) in the acute period that required urgent intervention such as hypertonic solutions, cerebral spinal fluid drainage, or surgical decompression. Elevated ICP requiring intervention was the only statistically significant risk factor, after correction, for the development of remote seizures ($P$ = 0.03) or epilepsy ($P$ = 0.04). None of the following were risk factors for either remote seizures or epilepsy: seizure during the first 7 days, etiology or location of ICH, use of seizure medications, or epileptiform discharges on EEG.

■ **COMMENTARY**

This relatively large, prospective study provides additional evidence that children with ICH, and in particular neonates, are more likely to present with seizures in the acute period than adults. The strongest risk factor for predicting epilepsy was elevated ICP requiring intervention. It is unclear whether elevated ICP was merely a proxy for the severity of the bleed, or if perhaps this represented a "second hit" to a brain already at risk for developing seizures.

It is interesting to note that although both infants and children had similar incidence of seizures during the first 7 days after ICH, the non-neonates were 2-3 times more likely to develop remote seizures or epilepsy. The use of antiseizure medication did not seem to prevent remote seizures or epilepsy. However, medication use and choice of drug was not uniform, and subgroup analysis was limited by the relatively small size of the subgroups. How seizures can best be prevented in children with ICH will require randomized controlled studies. But it is clear that the risk of seizure extends beyond the acute period, and further studies will hopefully provide additional data about which children are most at risk. ■

# Nocturnal Leg Cramps

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:*** *Nocturnal calf cramps are usually benign and respond to stretching and muscle-strengthening exercises.*

**Source:** Hawke F, et al. Factors associated with night-time calf muscle cramps: A case-control study. *Muscle Nerve* 2013;47;339-343.

PRESENT IN NEARLY 50% OF THOSE OLDER THAN 50 YEARS of age, increasing in prevalence with increasing age, and affecting both sexes equally, nocturnal leg cramps occur at least thrice weekly in 40%, and nighty in 5-10% of affected patients, producing pain while disrupting sleep. Lasting seconds to minutes and most commonly affecting the foot, calf, or thigh, forceful stretching of the affected muscles offers relief, and workup for underlying causes is usually in vain. What factors are associated with nocturnal calf cramps that might be etiologically important and amenable to therapeutic intervention?

Between August 2010-October 2011, 160 adults — 80 with nocturnal calf cramps and 80 age- and gender-matched controls without nocturnal calf cramps — were recruited from the Newcastle, Central Coast, and Hunter Valley regions of New South Wales, Australia, to undergo clinical evaluation and completion of a self-report survey. Exclusionary criteria encompassed neuromuscular or neurologic disease, pregnancy, dialysis, dementia, or leg injury that precluded participation in clinical testing. Clinical evaluation included testing ankle and toe strength, ankle and knee flexibility, toe sensation to 10-g filament and 64-Hz/c128-Hz graded tuning fork, and measurement of hallux blood pressure. Self-reported survey items included, but were not limited to, smoking history, alcohol intake, diet, fluid consumption, exercise, showering and sleeping habits, presence of varicose veins, use of compression stockings or high heels, medication and surgical history as indicators of general health, presence of back pain or sciatica, depression, diabetes, renal failure, or rheumatoid arthritis. Statistical analyses encompassed the Kolmogorov-Smirnov test, parametric and nonparametric tests, Spearman rho, chi-square, and Fisher exact tests, and significance was set at the 95% confidence interval.

Ankle weakness (inversion, eversion, dorsi- and plantar flexion), hallux weakness, tip-toe walking difficulty, tight hamstrings, muscle twitches, feet or leg tingling, cold feet in bed at night, increased fluid consumption, calf pain, and decreased migraine prevalence were significantly associated with nocturnal calf cramps, and logistic regression modeling identified only muscle twitching, leg tingling, and weak ankle dorsiflexion, but not diabetes or sensory deficits, as independent correlates of nocturnal calf cramps. Intermittent claudication, smoking, or alcoholism were not associated with nocturnal calf cramps, supporting a neurologic origin of this phenomenon.

## ■ COMMENTARY

Several non-pharmacologic therapies, including hydration, stretching, massage therapy, and herbal remedies are recommended for nocturnal calf cramps but none are

of proven efficacy. Pharmacologic treatment traditionally included quinine, now in disfavor due to serious adverse effects in 2-4%, including thrombocytopenia, hemolytic uremic syndrome, cardiac arrhythmias, and hypersensitivity reactions. Gabapentin, diphenhydramine, vitamin E or B complex, and calcium channel blockers (verapamil or diltiazem) may be useful, but have limited data to support their use. Baclofen is a favorite among Canadian neurologists.[1] ■

### Reference


1. Lim Fat mJ, et al. n eurologist practice patterns in treatment of muscle cramps in c anada. *J Foot Ankle Res* 2013;6:2. Available at: http://www.jfootankleres.com/content/6/1/2.


## CME Objectives

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

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

## CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
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## CME Questions

**1. Which of the following statements regarding cognitive dysfunction and contact sports is most true?**
   a. Athletes who sustain multiple concussions during contact sports suffer no cognitive dysfunction.
   b. Athletes who sustain multiple concussions during contact sports suffer cognitive dysfunction that is predominantly related to executive sequencing.
   c. Athletes who sustain multiple concussions during contact sports suffer cognitive dysfunction that includes difficulties in naming, word finding and episodic memory and also neurobehavioral changes such as depression.
   d. Athletes who sustain multiple concussions during contact sports suffer cognitive dysfunction but have no abnormalities on neuroimaging studies.

**2. What secondary endpoint did *not* show a benefit when combining interferon and glatiramer acetate?**
   a. CUA: sum of new enhanced lesions and new or enlarged unenhanced T2 lesions
   b. New enhancing lesions
   c. Progression on EDSS
   d. Disease activity-free status
   e. None of the above

**3. Vascular risk factors have no relationship to the development of dementia.**
   a. True
   b. False

**4. Which of the following increased the risk of developing epilepsy in children and infants with an intracerebral hemorrhage?**
   a. Seizures during the acute period
   b. Etiology of the hemorrhage
   c. Location of the hemorrhage
   d. Epileptiform discharges on EEG
   e. None of the above

**5. Logistic regression modeling identified which of the following as independent correlates of nocturnal calf cramps?**
   a. Muscle twitching
   b. Leg tingling
   c. Weak ankle dorsiflexion
   d. All of the above
   e. None of the above

**6. Patients with atrial fibrillation who are taking warfarin have no further risk of ischemic stroke.**
   a. True
   b. False

**7. Basilar artery occlusion usually has a poor prognosis for recovery, regardless of the type of treatment.**
   a. True
   b. False

**8. It is rare for patients to develop chronic pain syndromes after ischemic stroke.**
   a. True
   b. False

**In Future Issues:**

**Update on Pain Mechanisms**

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# Do Perioperative Beta-Blockers Reduce Mortality?

***In this issue:*** Beta-blockers and noncardiac surgery; prenatal medication exposure and risk of autism; reasons for statin discontinuations; and FDA actions.

## Perioperative beta-blockers

The use of perioperative beta-blockers has been debated for decades. Now, a large study from the U.S. Department of Veterans Affairs (VA) suggests that the drugs may be of benefit in selected patients. In a retrospective cohort analysis, exposure to beta-blockers on the day of or the day following noncardiac surgery was evaluated among a population-based sample of nearly 137,000 patients from 104 VA medical centers. The main outcome was all-cause 30-day mortality and cardiac morbidity. Overall, 55,138 patients (40%) were exposed to beta-blockers, although the rate was nearly 68% in those undergoing vascular surgery. Exposure increased with increased cardiac risk factors. Death occurred in just over 1% of patients and cardiac morbidity occurred in just under 1%. Overall, exposure to beta-blockers was associated with a lower mortality (relative risk [RR] 0.73%; 95% confidence interval [CI], 0.65-0.83; $P < 0.001$; number needed to treat [NNT], 241). The effect was greater in patients with higher cardiac risk factors, which include high-risk surgery, cerebrovascular disease, ischemic heart disease, heart failure, diabetes, and renal insufficiency. When stratified by the revised Cardiac Risk Index variables, patients with two or more cardiac risk factors had a RR of 0.63 (95% CI, 0.50-0.80; $P < 0.001$; NNT, 105), with three risk factors the RR was 0.54 (95% CI, 0.39-0.73; $P < 0.001$; NNT, 41), and with four or more risk factors the RR was 0.40 (95%CI, 0.25-0.73; $P < 0.001$; NNT, 18). This effect was limited to patients undergoing nonvascular surgery. Beta-blocker exposure also significantly reduced the rate of nonfatal Q-wave infarction or cardiac arrest by 37%. The authors conclude that in patients undergoing noncardiac, nonvascular surgery, perioperative beta-blockers significantly reduced 30-day all-cause mortality in patients with two or more cardiac risk factors and support the use of the drugs in these patients. They also suggest a multicenter randomized trial to assess the benefit in patients with low-to-intermediate risk. The authors were unable to find a benefit in stroke risk or in patients undergoing vascular surgery. They were also unable to determine if various beta-blockers (such as metoprolol vs atenolol) were of benefit or if the benefit was from various dosing regimens. (*JAMA* 2013; 309:1704-1713). ■

## Medication use and pregnancy

Two studies suggest that certain medications used during pregnancy may increase the risk of autism in offspring. In the first, which looked at antidepressants in pregnancy, researchers from Sweden reviewed the records of 4429 children with autism spectrum disorder (ASD) as well as 43,000 age- and sex-matched controls. A history of maternal, but not paternal, depression was associated with an increased risk of ASD and the association was confined to women reporting anti-

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depressant use during pregnancy (adjusted odds ratio 3.34; 95% CI, 1.50-7.47; $P = 0.003$). This association was irrespective of whether serotonin reuptake inhibitors or non-selective monoamine reuptake inhibitors (tricyclic antidepressants) were used. The association was confined to autism without intellectual disability. Still, the use of antidepressants accounted for only 0.6% of cases of ASD during the study, so the drugs were "unlikely to have contributed significantly towards the dramatic increased prevalence of autism spectrum disorders" (*BMJ* 2013;346:f2059). In the other study, researchers from Denmark reviewed the records of children exposed in utero to valproate (used to treat seizures and other neuropsychological disorders in mothers). Of more than 655,000 children born between 1996 and 2006, 5437 identified with ASD, including 2067 with childhood autism. The overall risk of autism in all children was 1.53%, but of the 508 children exposed to valproate, the absolute risk was 4.42% (95% CI, 2.59-7.46%) for ASD and 2.50% (95%CI, 1.30-4.81%) for childhood autism (adjusted hazard ratio, 5.2). The risk was similar regardless of the indication for use of valproate in the mother. These findings suggest that maternal use of valproate significantly increases the risk for ASD and childhood autism in offspring. The authors suggest that a risk-benefit analysis should be considered for women on valproate in their childbearing years (*JAMA* 2013;309:1696-1703). ■

## Discontinuation of statins

Most patients who stop statins due to side effects will tolerate the drugs if rechallenged, according to the findings of a new study. In a retrospective cohort study using data from two Boston hospitals, researchers reviewed the records of nearly 108,000 patients on statins and found statin-related events such as muscle pain documented in 18,778 (17.4%). Of those patients, 11,124 stopped the drugs at least temporarily and 6579 were restarted within the subsequent 12 months. The vast majority of patients restarted on a statin tolerated the drug (92.2%), although about half were eventually switched to a different statin. The authors conclude that statin-related side effects are common and often lead to discontinuation; however, most patients who are rechallenged can tolerate statins long-term. They suggest that "statin-related events may have other causes, are tolerable, or may be specific to individual statins rather than the entire drug class" (*Ann Intern Med* 2013;158:526-534). ■

## FDA actions

The FDA has updated labeling of the new tamper-proof oxycodone (OxyContin), while at the same time denying approval of generic forms of the original formulation of oxycodone. The new labeling indicates that the product "has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (snorting)." The agency's refusal to approve generic forms of the original formulation was based on the increased risk of abuse inherent in the non-tamper proof form leading to the risk of serious adverse events including overdose and death. Because of this, the agency has determined that the benefits of the original OxyContin and its generics no longer outweigh its risks and it has been withdrawn from sales. The new tamper-proof formulation is more difficult to crush, break, or dissolve. If tampered with, it forms a viscous hydrogel that cannot be easily injected or snorted. Oral abuse is still possible.

The FDA has approved a fixed combination of doxylamine succinate and pyridoxine for the treatment of nausea and vomiting due to pregnancy. This is a reintroduction of a product widely used between 1956 and 1983. Then marketed as Bendectin, the product was voluntarily withdrawn by the manufacturer due to lawsuits related to birth defects, although evidence of risk was not supported by scientific evidence. The reapproval was based on a study of 261 women experiencing nausea and vomiting due to pregnancy in which the drug was more effective than placebo in relieving symptoms. Since the 1980s, observational studies have shown that doxylamine and pyridoxine do not pose an increased risk of harm to the fetus. The recommended starting dose is two tablets taken at bedtime on an empty stomach. The combination is marketed by Duchesnay Inc. as Diclegis.

The FDA has approved prothrombin complex concentrate for the rapid reversal of anticoagulation by warfarin and other vitamin K antagonists. Plasma is the only other option for this use currently available, and prothrombin complex can be given at significantly lower volume than plasma. The product is made from pooled plasma of healthy donors that is processed to minimize the risk of viral and other diseases. The approval was based on a study of 216 patients who were anticoagulated and had major bleeding. Plasma complex concentrate was found to be similar to plasma in its ability to stop major bleeding. Plasma complex concentrate is marketed by CSL Behring as Kcentra. ■

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By Louis Kuritzky, MD

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## Risks and Benefits of an Extended 10-year Tamoxifen Regimen for Breast Cancer

**Source:** Davies C, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of estrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805-816.

THE PREVAILING 5-YEAR TAMOXIFEN REGIMEN for breast cancer has been shown to reduce breast cancer mortality by as much as one-third over a 15-year interval; a comparison with a shorter regimen (1-2 year) found the longer duration to be superior. Would even longer tamoxifen administration (i.e., > 5 years) provide even greater risk reduction of breast cancer and its consequences, and if so, would longer regimens induce greater toxicity to other non-targeted tissues (e.g., induction of endometrial cancer)?

The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial randomized women with estrogen receptor-positive breast cancer (B-CA) to either 5 years (n = 3418) or 10 years (n = 3428) of tamoxifen. Follow-up continued for 5 years after conclusion of the 10-year tamoxifen course. The estrogen-receptor positive B-CA group actually represents only about half of all of the women enrolled in ATLAS; the estrogen-receptor negative population of ATLAS demonstrated no risk reduction through longer tamoxifen administration.

Numerous outcomes favored 10-year tamoxifen over 5 years and were statistically significant: B-CA recurrence (617 vs 711 cases), B-CA mortality (639 vs 722 deaths), and ischemic heart disease death or hospitalization (127 vs 163 cases). On the negative side of the equation, all-cause mortality was not impacted by the longer tamoxifen regimen, and there was a significant increase in pulmonary embolism (41 vs 21 cases) as well as endometrial cancers (116 cases vs 63 cases).

These results were apparently sufficiently impressive enough to make the cover story in the *Lancet*. Your reviewer, however, takes pause at the fact that — similar to the situation with results for prostate cancer screening, which has recently been diminished by convincing evidence that screening may reduce prostate cancer mortality but not total mortality — a 10-year tamoxifen regimen reduces B-CA mortality but not total mortality, and has not-insubstantial adverse effects as well as costs. ■

## Is There More Pro than Con in Probiotics in Critically Ill Adults?

**Source:** Barraud D, et al. Impact of the administration of probiotics on mortality in critically ill adult patients. *Chest* 2013; 143:646-655.

THE TECHNICAL DEFINITION OF PROBIOTIC offered by the World Health Organization and the Food and Agriculture Organization sounds promising enough: "viable microorganisms that, when ingested in a sufficient amount, can be beneficial for health." Unfortunately, the existing literature on the benefits of probiotics is not quite so convincing.

Barraud et al performed a meta-analysis of randomized, controlled trials published between 1950-2012 in which probiotics were used in the intensive care unit (ICU) setting, ultimately netting 13 clinical trials, all published after 2002 (n = 1439). The probiotic used in each of these trials was in the *Lactobacillus* family, and although some trials used only one *Lactobacillus* strain, several trials used mixed strains of *Lactobacilli*. Endpoints included ICU mortality, hospital mortality, ICU infections, incidence of diarrhea, and duration of mechanical ventilation.

Of the above-mentioned endpoints, a statistically significant favorable odds ratio was seen only for the incidence of ICU-acquired pneumonia, even though the overall larger category of ICU-acquired infections was not statistically significantly improved. Although the failure to achieve significance to numerous endpoints is disconcerting, the authors point out that since probiotic administration is generally safe, the favorable impact on ICU-acquired pneumonia (a reduction of approximately 40%) might prompt consideration for use in patients known to be particularly at risk for this consequence. ■

## Are OSA Outcomes Better in the Hands of Sleep Specialists than Primary Care Clinicians?

**Source:** Chai-Coetzer CL, et al. Primary care vs specialist sleep center management of obstructive sleep apnea and daytime sleepiness and quality of life: A randomized trial. *JAMA* 2013;309:997-1004.

THE RECOGNITION OF OBSTRUCTIVE SLEEP apnea (OSA) as a health burden of compelling epidemiologic presence with significant impact on both quality of life

and cardiovascular health has been recognized by health care providers of essentially all disciplines. Increasingly, sophisticated sleep laboratory monitoring devices allow ever more detailed (and usually more costly) understanding of sleep dysregulation. At the same time, awareness of the frequency and consequences of OSA among diverse disciplines of medicine has resulted in a sufficiently burgeoning population of individuals who merit screening that sleep labs are often unable to keep pace with the increasing demand.

A proliferation of simpler, home-based tools for the identification and potential management of OSA that can be used by sleep specialists and primary care clinicians alike has prompted the question of whether outcomes for OSA patients attended by sleep specialists (who are usually not primary care clinicians), typically with complex sleep analysis tools (which are most commonly employed in a specific sleep laboratory), are superior to outcomes for patients attended by primary care clinicians with less sophisticated home-based tools.

The authors report on a randomized, controlled, non-inferiority trial of patients with OSA identified and treated either in a university sleep laboratory by sleep specialists or by community primary care practices. The primary outcome was improvement in the Epworth Sleepiness Scale, a commonly used and validated scoring system for monitoring sleepiness associated with OSA.

At the end of the 6-month trial, scores on the Epworth Sleepiness Scales were identical in both groups, and outcomes in the primary care group were determined to be non-inferior to sleep specialist care. Hopefully, primary care clinicians will become more involved in the identification and management of OSA, since equally salutary outcomes are seen in their hands as in the hands of sleep specialists. ■

## Inhaled Steroids Increase Risk of TB in COPD Patients

**Source:** Kim J, et al. Inhaled corticosteroid is associated with an increased risk of TB in patients with COPD. *Chest* 2013; 143:1018-1024.

Reactivation of tuberculosis (TB) is an ongoing concern among patients who receive immunosuppressive agents such as TNF-alpha agents for rheumatoid arthritis. Similarly, long-term use of systemic steroids (i.e., ≥ 30 days) in amounts as small as 7.5 mg/day of prednisone increases the risk of TB. Inhaled corticosteroids (ICS) have been associated with systemic effects such as growth retardation (in asthma), reduced bone mineral density, and increased risk of pneumonia (in chronic obstructive pulmonary disease [COPD]). Whether ICS might also be associated with risk for development or reactivation of TB has not been fully clarified.

Kim et al performed a retrospective analysis of COPD patients (n = 620) in a university hospital in South Korea (where the background prevalence of TB is substantially greater than many other nations) to compare the rate of TB activation in persons who had received ICS with controls. To eliminate the confounding factor of systemic steroid use, COPD patients who had received ≥ 7.5 mg for 1 month or more were excluded from the analysis.

There was a substantially greater and statistically significant risk for development of active TB among COPD patients who had been treated with ICS (hazard ratio = 9). In patients whose baseline chest x-ray showed evidence of prior (but quiescent) TB, the hazard ratio for activation of TB was 25!

Although the prevalence of TB is much greater in Korea than in the United States, these data suggest greater vigilance for TB activation in patients chronically using ICS, especially if their x-rays indicate evidence of prior TB. ■

## The ASH Position Paper on Orthostatic Hypotension

**Source:** Shibao C, et al. ASH position paper: Evaluation and treatment of orthostatic hypotension. *J Clin Hypertens* 2013;15:147-153.

Standing from a seated or supine position is normally associated with minimal, if any, blood pressure (BP) change, thanks to homeostatic mechanisms that alter splanchnic and peripheral blood compartments by selective intravascular redistribution and vascular tone. When BP change upon standing exceeds 20/10 mmHg, a diagnosis of orthostatic hypotension (OH) is established. Although tilt-table testing is often suggested for formal diagnosis, simple office measurement of BP 1-3 minutes after standing suffices.

Although sometimes OH produces minor distracting symptoms of dizziness that may be diminished by standing slowly, leg crossing, maintenance of good fluid balance, etc., it can also be a cause of falls, with anticipatable subsequent catastrophes such as hip fracture. Additionally, OH epidemiological data have noted an association between OH and stroke.

A variety of commonly used medications can precipitate or exacerbate OH, including alpha blockers, diuretics, vasodilators, dopamine agonists, and tricyclic antidepressants, modulation of which may OH improve symptoms. Pharmacologic treatments for OH include fludrocortisone (to increase intravascular volume), midodrine (a short-acting vasopressor agent), and other sympathomimetic agents.

OH is also seen in several primary neurologic disorders such as Parkinson's disease, multiple system atrophy, and Lewy body dementia.

Clinicians should suspect OH particularly in patients who report dizziness, unexplained falls, or syncope, although even symptoms such as blurred vision or neck/shoulder pain ("coat hanger" distribution pain) may reflect OH. Fortunately, a variety of lifestyle and pharmacologic treatments can be helpful. ■

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