NEUROLOGY ALERT®
Providing Evidence-based Clinical Information for 32 Years
A monthly survey of developments in neurologic medicine
AHC Media LLC Home Page—www.ahcmedia.com
CME for Physicians—www.cmeweb.com

AHC Media

INSIDE

Financial Disclosure: *Neurology Alert's* editor in chief, Matthew Fink, MD, is a retained consultant for MAQUET. Peer reviewer M. Flint Beal, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Post-Radiation Motor Neuron Disease

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: *Post-radiation lower motor neuron disease mimics spinal muscular atrophy rather than classical amyotrophic lateral sclerosis.*

Source: Abraham A, Drory VE. Postradiation lower motor neuron syndrome: Case series and literature review. *J Neurol* 2013;260:1802-1806.

If included in the treatment field, radiation therapy can cause injury to the central or peripheral nervous system that may occur during the course of therapy (acute), within weeks to 3 months (early delayed), or beyond 3 months (delayed). Spinal cord syndromes include a self-limited transient myelopathy occurring 2-6 months following spinal cord irradiation, characterized by the development of Lhermitte's sign, resolving spontaneously within a year, and attributed to reversible demyelination of the posterior columns of the spinal cord. It does not presage chronic progressive myelitis. More disabling consequences of spinal cord irradiation include acute paralysis due to cord ischemia, intramedullary spinal cord hemorrhage, and a lower motor neuron syndrome; the latter is due to involvement of either the anterior horn cell or cauda equina and is the subject of this case series.

Medical records of patients seen between 2005-2012 with a lower-limb, post-radiation, lower motor neuron syndrome were reviewed. Inclusion criteria encompassed the presence of slowly progressive leg weakness in a patient with prior distal spinal cord and cauda equina radiation; signs of lower motor neuron involvement including fasciculations, muscle atrophy, and depressed or absent deep tendon reflexes; and electrophysiological studies demonstrating denervation in leg muscles. Spinal imaging and cerebrospinal fluid (CSF) studies had to be normal, except for the inclusion of patients with elevated CSF protein, and no alternative diagnosis could be present. Similar patients found by PubMed review of the literature were included for analysis.

VOLUME 32 • NUMBER 1 • SEPTEMBER 2013 • PAGES 1-8

NOW AVAILABLE ONLINE
www.ahcmedia.com

Five patients were identified and supplemented by 45 similar cases found in the literature. Among the five cases, three underwent distal spinal cord and cauda equina irradiation for seminoma and two for lymphoma. Total radiation dosage for the two patients on whom it was available was 2500 cGy and 2800 cGy, and the mean latency to onset of symptoms was 15 years (range 10-19 years). Distal weakness, bilateral (n = 3) or unilateral (n = 2), with depressed or absent reflexes were the characteristic findings, with two patients having thigh fasciculations and two noting a subjective, stocking distribution, sensory disturbance, objectively documented in only one patient, expressed as decreased light touch. None had sphincteric symptoms, and all continued to slowly deteriorate but remained ambulatory. Nerve conduction studies revealed low motor amplitudes in four patients and sensory abnormalities in only one, with positive sharp waves, large polyphasic motor units, and a decreased interference pattern on needle electromyography, predominantly in L4-5-S1 myotomes. Among 45 patients collected from the literature, mean age was 33 years, average radiation dose was 5225 cGy, and mean latency to symptom onset was 9 years (range 3 months to 27 years). Males predominated (89%), with testicular cancer (67%) and lymphoma (23%) accounting for the majority of cases, and 10% due to cancer of the kidney, cervix, or breast; pheochromocytoma; or medulloblastoma. Among 16 patients who underwent spinal MRI, seven showed gadolinium enhancement of the cauda equina. Sensory nerve conduction studies were normal in 96% of patients.

Neurology Alert, ISSN 0741-4234, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie G. Coplin
MANAGING EDITOR: Neill L. Kimball
INTERIM EDITORIAL DIRECTOR: Lee Landenberger

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Neurology Alert,*** P.O. Box 105109, Atlanta, GA 30348.

Back Issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: leslie.coplin@ahcmedia.com
Online: www.ahcmedia.com

Subscription Prices

United States
1 year with free AMA Category 1 credits: $369
Add $17.95 for shipping & handling.
(Student/Resident rate: $125)

Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Canada
Add 7% GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of *25 AMA PRA Category 1 Credits™.* Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the neurologist. It is in effect for 36 months from the date of the publication.

AHC Media

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

■ **COMMENTARY**

Post-radiation lower motor neuron disease mimics sporadic progressive spinal muscular atrophy (PSMA), which itself is incorrectly diagnosed in up to 20% of cases. As several of these mimics are treatable, correct diagnosis is imperative.[1] Multifocal motor neuropathy with conduction block is the disorder most often mistaken for PSMA, but, in addition to post-radiation lower motor neuron disease, other mimics include chronic inflammatory demyelinating polyneuropathy, inflammatory myopathy, myasthenia gravis, myopathy, syringomyelia, and idiopathic chronic axonal neuronal neuropathy. When the upper limbs and/or cranial muscles are involved, Hirayama's disease, brachial neuritis, Kennedy's syndrome, and distal myopathy or inclusion body myositis are other considerations. ■

Reference

1. Visser J, et al. Mimic syndromes in sporadic cases of progressive spinal muscular atrophy. *Neurology* 2002;58:1593-1596.

Multiple Sclerosis Risk After Childhood Optic Neuritis

ABSTRACT & COMMENTARY

By Wendy S. Vargas, MD

Instructor in Neurology in Pediatrics, Weill Cornell Medical College

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

Synopsis: *Similar to adults, children with brain MRI abnormalities and positive oligoclonal bands at onset of optic neuritis are at high risk of developing multiple sclerosis.*

Source: Heussinger N, et al. Predicting multiple sclerosis following isolated optic neuritis in children. *Eur J Neurol* 2013;20:1292-1296.

Optic neuritis is a common initial manifestation of multiple sclerosis (MS). Based on the Optic Neuritis Treatment Trial (ONTT), the 10-year risk of developing MS following optic neuritis is 56% if the baseline MRI shows a single brain lesion.[1] However, this trial is not generalizable to children because only patients 18 years or older were included. Given the limited data in calculating pediatric MS risk, Heussinger et al recently reported on the role of brain MRI, oligoclonal bands (OCB), and visual evoked potentials (VEPs) as predictive markers for MS in children with optic neuritis.

This retrospective study included children between 4

and 17 years of age. Thirty-four children with isolated optic neuritis were identified from a pool of 159 total patients presenting with rapid onset visual failure. The authors used the 2005 McDonald criteria for the diagnosis of MS. Data were collected from the patient's medical record or via telephone contact with the patient. MRI of the brain, VEPs, and lumbar puncture for examination of OCB were performed in all 34 children at onset of optic neuritis. Using the 2005 McDonald criteria, nine of the 34 patients converted to clinically definite MS. The authors analyzed whether age, sex, follow-up time, pathological VEPs at baseline, optic neuritis type (unilateral, bilateral, or recurrent), cranial MRI at baseline, and OCB at baseline could predict MS in this subgroup of patients. Following univariate analysis, only abnormal brain MRI and the presence of OCB were identified as significant predictors of disease progression to MS (odds ratio [OR], 20.5; 95% confidence interval [CI], 2.15-196.1; and OR, 12.0; 95% CI, 0.23-8.2, respectively). When multivariate analysis was performed, only abnormal brain MRI at baseline remained a statistically significant predictor of progression to MS (OR, 19.9; 95% CI, 1.8-219). VEPs at baseline were not a statistically significant predictor.

■ COMMENTARY

The rate of conversion to MS after childhood clinically isolated syndrome has not been clearly defined. This is the first study to specifically analyze the utility of brain MRI, OCB, and VEPs for predicting progression to clinically definite MS in children with optic neuritis. Clinically, such information is invaluable. As neurologists caring for these children, surely we will be asked to comment on this risk. This study lends credence to the importance of obtaining MRI and OCB after initial presentation with optic neuritis in children. Not surprisingly, these same tests are useful for risk stratification in older patients. In adults with optic neuritis, the presence of white matter lesions on brain MRI and OCB in the cerebrospinal fluid (CSF) were identified as risk factors for the development of MS by the ONTT study group.[1] The results of the current study confirm the predictive value of brain MRI and OCB in optic neuritis patients under the age of 18. VEPs did not predict which children went on to develop MS after isolated optic neuritis. Similar VEP findings have been reported in adults.

A major strength of this study lies in the long-term follow-up of these children (mean 5 years), allowing for a quantitative MS risk prediction model after optic neuritis in a child. Nevertheless, the study is subject to certain limitations. First, it is a retrospective chart review. Moreover, for certain cases, data were obtained from the patient over the telephone and not the medical record. This study design can lend itself to recall bias. Second, selection bias is certainly a possibility as patients were screened from a child neurology unit and milder cases may not have been referred to a neurologist. Third, the small sample size led to very wide confidence intervals, making the real effects difficult to estimate reliably. Lastly, the authors claim that their findings have not been previously described in the literature. In a large, prospective, cohort study in a Canadian population of children with incident demyelination, MS was strongly associated with baseline MRI evidence of one or more brain lesions or CSF OCBs.[2] Nevertheless, the current data suggest that cranial MRI and OCB form the basis of a prediction model through which pediatric patients' risk of conversion to MS might be quantified. Large, multicenter, prospective studies in this area are needed. ■

References

1. Beck RW, et al. High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: Experience of the Optic Neuritis Treatment Trial. *Arch Ophthalmol* 2003;121:944-949.
2. Banwell B, et al. Clinical, environmental and genetic determinants of multiple sclerosis in children with acute demyelination: A prospective national cohort study. *Lancet Neurol* 2011;10:436-445.

Diffusion-Tensor Magnetic Resonance Imaging in Tau-Related Neurodegenerative Diseases

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: *Diffusion-tensor MRI can reliably distinguish amyloid-associated neurodegenerative disorders, such as Alzheimer's disease, from tau-associated disorders, such as corticobasal gangionic degeneration and progressive supranuclear palsy.*

Source: Sajjadi SA, et al. Diffusion tensor magnetic resonance imaging for single subject diagnosis in neurodegenerative diseases. *Brain* 2013:136:2253-2261.

A MAJOR FRUSTRATION IN THE DIAGNOSIS OF NEURODEGENerative disorders is the paucity of biomarker tests. Amyloid PET and CSF A-beta and tau analysis now provide ways to assess Alzheimer's disease (AD) pathophysi-

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*

Recanalization of Basilar Artery Occlusion May Be Beneficial Up to 48 Hours After Onset of Symptoms

Source: Strbian D, et al. Thrombolysis of basilar artery occlusion: Impact of baseline ischemia and time. *Ann Neurol* 2013;73:688-694.

It is unclear how long one can wait before attempting intra-arterial interventions in patients with basilar artery occlusion. Neurologists at Helsinki University, Finland, prospectively evaluated 184 consecutive patients with angiographically proven basilar artery occlusion. The majority of these patients received intravenous alteplase and concomitant heparin before the intervention. Baseline ischemia was defined as an Acute Stroke Prognosis Early CT Score (ASPECTS) < 8. Onset of symptoms to treatment time was evaluated as a variable from 0 hours to 48 hours. Successful recanalization was defined as attaining a TIMI score of 2 to 3. Poor 3-month outcome was evaluated and defined as a modified Rankin score of 3 to 6.

Ninety-six percent of the patients with baseline ASPECTS score < 8 had a poor 3-month outcome, and a similar number, 94%, was observed in those with confirmed recanalization. In contrast, half of the patients with ASPECTS score > 8 and successful recanalization achieved a good outcome. Of note, onset of symptoms to treatment time, as a variable, was not associated with poor outcome in any of the analyses. The factors independently associated with poor outcome were older age, high baseline NIH Stroke Scale, lack of recanalization, history of atrial fibrillation, and asymptomatic intracerebral hemorrhage.

Based on this single-center prospective study, it appears that in the absence of extensive baseline ischemia, recanalization of basilar artery occlusion can be

ology in vivo, but similar tests are lacking for other common neurodegenerative diseases, since there are currently no ligands for inclusions composed of tau, TDP-43, alpha-synuclein, etc.

An interesting study by Sajjadi and colleagues suggests that abnormalities on diffusion tensor magnetic resonance imaging (DTI) may be sensitive and specific for corticobasal ganglionic degeneration (CBGD) and progressive supranuclear palsy (PSP). They performed DTI on nine patients with progressive nonfluent aphasia (PNFA, all of whom later met clinical criteria for CBGD or PSP), nine patients with AD, nine patients with semantic dementia (SD), and 26 control subjects. MRIs were performed at 3 tesla, with diffusion measured in 63 directions.

Remarkably, the PNFA (CBGD/PSP) subjects all showed a qualitatively distinct pattern of DTI abnormalities that completely separated them from the AD, SD, and control groups, without any overlap. All PNFA (CBGD/PSP) subjects showed increased radial diffusivity and decreased fractional anisotropy throughout essentially all the white matter of the hemispheres. This pattern was seen even in PNFA subjects with very mild symptoms. None of the AD or SD subjects showed this pattern of diffuse white matter involvement. As expected, AD subjects had patchy DTI abnormalities in posterior cingulate and parieto temporal white matter, and SD subjects had abnormalities in anterior temporal white matter. Because there was no overlap between the PNFA (CBGD/PSP) group and the other groups, a pattern of DTI abnormalities throughout all the white matter of the hemispheres might potentially be useful in diagnosing CBGD/PSP at the level of individual subjects.

■ COMMENTARY

However, a number of caveats are in order. First, pathological verification of diagnosis was obtained in only one case. Diagnosis was made clinically in all other cases. Thus, the clear distinction in DTI abnormalities between CBGD/PSP and other groups thus far only has been seen in cases where the clinical classification is evident. Whether the DTI pattern holds in cases where the clinical classification is ambiguous remains to be seen. Second, subjects with white matter abnormalities on T2 images were excluded. Unfortunately, such abnormalities are quite common, so replication with subjects having these abnormalities will be important. Third, it is still unclear whether these findings are dependent on technical details of the DTI acquisition — magnet strength, resolution, directions, etc. Fourth, the pathological basis for the diffuse DTI abnormalities seen in the CBGD/PSP cases is unknown. The authors speculate that they are due to glial pathology rather than axonal abnormalities.

beneficial up to 48 hours after onset of symptoms with good outcomes demonstrated in 50% of patients. ■

Non-Dominant Hemisphere Ischemic Stroke May Impair Affective Empathy

Source: Leigh R, et al. Acute lesions that impair affective empathy. *Brain* 2013;136:2539-2549.

Empathy, defined as the ability to make inferences about what other people think and feel, is an elusive quality that is rarely assessed in patients who present with acute stroke. Several important neurological disorders are known to disrupt various aspects of empathy, including autism, frontotemporal dementia, traumatic head injury, and schizophrenia. In functional imaging studies using functional MRI of healthy participants, as well as previous lesion studies, a distinct neural network has been defined that plays a role in empathy — the prefrontal cortex, orbitofrontal gyrus, anterior insula, anterior cingulate cortex, temporal pole, amygdala, and the temporal parietal junction. The authors of this study hypothesized that right-sided lesions to the brain would cause impaired affective empathy, and they studied 27 patients with acute right hemisphere ischemic strokes and 24 neurologically intact patients on a test of affective empathy.

Acute impairment of affective empathy was identified in patients who had infarcts in the hypothesized network as noted above, particularly in lesions that involve the left anterior temporal pole and the anterior insula. Patients who had impaired empathy also had impaired comprehension of affective prosody, and had difficulty in understanding the affective nature of speech when they communicated with others. Patients with impaired empathy did not show any difference in performance on tests of hemispatial neglect, the volume of infarcts, or sex distribution, compared to controls. Impaired empathy is a subtle manifestation of non-dominant hemisphere ischemic stroke, and should be evaluated and assessed as part of a comprehensive neurocognitive battery for patients who have had ischemic stroke. ■

If these issues can be resolved, DTI may become a useful biological test to aid in diagnosis of neurodegenerative disorders. ■

Dopaminergic Therapy for the Treatment of Restless Legs Syndrome During Pregnancy

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD, PhD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Henchcliffe reports she is on the speakers bureau and advisory board for Allergan and Teva; speakers bureau for Boehringer-Ingelheim, GlaxoSmithKline, and Novartis; advisory board for Merz; and is a consultant for Gerson Lehman Group and Guidepoint Global.

Synopsis: *This small, prospective case series evaluated pregnancy outcomes of women who took levodopa, pramipexole, ropinirole, and rotigotine for treatment of restless legs syndrome during pregnancy. No major birth defects were identified with any of the treatments.*

Source: Dostal M, et al. Pregnancy outcome following use of levodopa, pramipexole, ropinerole, and rotigotine for restless legs syndrome during pregnancy: A case series. *Eur J Neurol* 2013;20:1241-1246.

The primary purpose of this study was to assess the safety of dopamine agonist exposure during pregnancy, in particular as it relates to treatment of restless legs syndrome (RLS). Data were collected by the Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy between 1998 and 2011 via surveys of women identified through direct or physician contact. In cases of use of levodopa, pramipexole, ropinirole, and rotigotine during pregnancy, questionnaire or phone interview at time of contact and follow-up data at 8 weeks after the expected delivery date were obtained. The primary outcomes were rates of pregnancy loss and major birth defects (structural abnormalities of medical, surgical, or cosmetic relevance). Sixty-seven relevant exposures were evaluated, with 59 women completing follow-up, of whom 42 were exposed to levodopa (four in combination with dopamine agonist), 15 to pramipexole, four to ropinirole, and two to rotigotine. Medication was mostly for RLS (n = 32), but also Parkinson's disease (n = 3), dopa-responsive dystonia (n = 4), dystonia (n = 2), and one case of a suicide attempt with extremely high levodopa exposure. All except three pa-

tients were exposed during at least the first trimester. The median daily dose of levodopa ranged from 100-1500 mg, and pramipexole from 0.8-1.0 mg daily (ranges were not provided for ropinirole and rotigotine). The major finding was that no major birth defects were reported in any group. Three of 42 levodopa-exposed pregnancies demonstrated minor abnormalities, comprising patent foramen ovale/patent ductus arteriosus, nose deformity, and clubfoot.

■ COMMENTARY

This paper addresses an important and difficult area of neurology — the risk of medical treatment during pregnancy. Insufficient data currently exist on the use of dopamine agonists during pregnancy to support well-informed treatment decisions for RLS. However, the prevalence of RLS during pregnancy is estimated at 12-26%, and symptoms may worsen as the pregnancy progresses, with significant impact on well being. There have been some data collected on the use of levodopa and the dopamine agonists pramipexole, rotigotine, and ropinirole during pregnancy in Parkinson's disease and dopa-responsive dystonia, but not in the more common condition of RLS. Therefore, most physicians recommend that these drugs be stopped during pregnancy in women with RLS. It is important to note that this case series did not demonstrate an increased risk of major or minor birth defects, premature birth, or fetal growth restriction in patients receiving levodopa or pramipexole. Unfortunately, although these data do add to our experience, the number of cases is too small to establish the safety of these drugs during pregnancy. Only 67 cases were identified during the 13 years of enrollment into the database. Other limitations include the reliance of data acquisition on voluntary reporting and the acquisition of follow-up data from physicians and patients. There is more published experience of cabergoline exposure in pregnancy, mostly during the first trimester, due to its use in treatment of hyperprolactinemia. However, in the United States, cabergoline is not approved for RLS, and of the three agonists that are approved (pramipexole, ropinirole, and rotigotine) only 21 such cases are included in this study. Gabapentin is also FDA-approved for moderate-to-severe RLS in the United States, but this database does not include relevant data. Finally, any discussion of iron deficiency is lacking, and in individuals with RLS this possibility needs to be tested and treated. For neurologists, this study provides modest data regarding the use of levodopa in RLS, but the authors do not recommend use of pramipexole, ropinirole, and rotigotine during pregnancy due to scarce information. This study should prompt further systematic data collection, but it does provide a modest platform for reassuring those inadvertently exposed to these medications during pregnancy. ■

Restless Legs Syndrome in Advanced Renal Disease

ABSTRACT & COMMENTARY

By Alexander Shtilbans, MD, PhD

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *Restless legs syndrome is prevalent in Taiwanese dialysis patients and is associated with type 2 diabetes, anemia, lower serum iron, and long duration of dialysis.*

Source: Lin CH, et al. Restless legs syndrome in end-stage renal disease: A multicenter study in Taiwan. *Eur J Neurol* 2013;20:1025-1031.

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by a distressing urge to move the legs, occasionally the arms, and is usually accompanied by uncomfortable sensations of pain in the affected body parts, mostly the legs. The sensations occur particularly in the evening or at night and are relieved by movements. RLS can be primary or secondary due to metabolic abnormalities. The pathophysiology of primary RLS is still poorly understood, but is thought to be related, at least in part, to dysfunction of the central dopaminergic system, iron metabolism, and/or central opioid neurotransmission. Secondary RLS is classically associated with iron deficiency anemia, pregnancy, or uremia in end-stage renal disease. The overall prevalence of RLS in the European and North American population is believed to be about 5%. While the prevalence of the primary RLS in Asian countries is less, secondary RLS, such as related to end-stage renal disease (ESRD), is more common in those populations.

The authors of this paper conducted a multicenter, case-control study aimed to investigate the prevalence of RLS in dialysis patients in Taiwan, a country with a high incidence of uremia, to study associated risk factors for RLS. They recruited 1130 patients with ESRD from 17 dialysis centers. Demographic data were collected, and evaluations by a nephrologist and a movement disorder neurologist were performed with a detailed questionnaire and clinical examination, followed by collection of blood samples. In cases where distal polyneuropathy was suspected, nerve conduction studies were performed.

They found that 286 patients (25.3%) had RLS, and those patients were more likely to have lower serum iron, type 2 diabetes, and neuropathy compared to patients without RLS. Nerve conduction studies confirmed polyneuropathy in 86 out of the 303 subjects suspected to have it. No other demographic factors or other comorbidities

were found to correlate with the prevalence of RLS. Patients with RLS had prolonged sleep-onset latency as a consequence of their RLS. A multivariate logistic regression analysis showed that a history of type 2 diabetes was significantly correlated with moderate to severe RLS (odds ratio [OR] = 4.04). Low hemoglobin level (OR = 5.41) and duration of dialysis (OR = 1.01) also showed significant correlations with the severity of RLS.

■ **COMMENTARY**

The prevalence of RLS in patients with end-stage renal disease varies widely in published series from 6-70%. The authors of this case-control study evaluated the prevalence and risk factors for RLS among dialysis patients in Taiwan. Besides establishing the prevalence of RLS in this population to be 25%, the authors found a high correlation with type 2 diabetes, low hemoglobin, and duration of dialysis. The authors propose that the great variation in prevalence of RLS in dialysis patients in different countries may be due to either genetic predisposition and/or differences in strategies for managing dialysis patients, and it is unclear whether RLS is associated with the dialysis procedure itself, or related, at least in part, to the advanced renal disease. The authors argue that the associated presence of diabetic neuropathy could be responsible for the increased prevalence of RLS in patients with type 2 diabetes, and the study might have underestimated the prevalence of peripheral neuropathy, since this diagnosis was only made upon confirmation with nerve conduction studies. A small fiber neuropathy may not be detected by nerve conduction studies and a skin biopsy is usually needed for the diagnosis. The authors further propose that there might be a decrease in central nervous system dopamine in patients with diabetes, which in turn could decrease central inhibition of the sensory input into the spinal cord, causing RLS symptoms. While these might be related, we know that not all Parkinson's disease patients, who clearly have dopamine deficiency, have RLS. A prospective cohort study of patients with mild-moderate renal disease would be useful to estimate at which point of their renal disease progression patients develop RLS and how much is related to dialysis. ■

Back to the Vascular Theory of Migraine?

ABSTRACT & COMMENTAEY

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a retained consultant for Boehringer Ingelheim and Bayer, and is on the speakers bureau for Boehringer Ingelheim.

Synopsis: *Nitric oxide donor vasoactive compounds may trigger migraine headaches in migraineurs by promoting a massive increase in the mechanosensitivity of meningeal nociceptors, through an intermediate vasodilatory effect on meningeal vasculature.*

Source: Zhang X, et al. Vascular extracellular signal-regulated kinase mediates migraine-related sensitization of meningeal nociceptors. *Ann Neurol* 2013;73:741-750.

THE MECHANISMS UNDERLYING THE PAIN OF MIGRAINE HEADache remain a mystery, with one possible component being increased mechanosensitivity, or sensitization, of nociceptive neurons that innervate the intracranial meninges. Nitroglycerin (NTG) and other nitric oxide (NO) donor vasoactive compounds can cause a delayed migraine-like headache in migraineurs. This delayed, NTG-induced headache responds to triptans and is associated with the inflammatory and neurotransmitter characteristics of migraine headaches. Systemic NTG administration and its delayed effects have been used as an experimental model of migraine headache in animals and humans. The finding that this NTG-induced headache is delayed for 3-4 hours after administration implies that NO acts as a trigger for a series of endogenous processes that eventually lead to pain sensitization.

The authors used a clinically relevant model of migraine triggering, infusion of NTG as an NO donor to examine the response properties of meningeal nociceptors. Single-unit recordings made in the trigeminal ganglion of male Sprague–Dawley rats were used to test changes in the activity and mechanosensitivity of meningeal nociceptors in response to administration of NTG or another NO donor, S-nitroso-N-acetyl-DL-penicillamine (SNAP), at doses relevant to the human model of migraine headache. Immunohistochemistry and pharmacological manipulations were used to investigate the possible role of meningeal vascular signaling in mediating the responses of meningeal nociceptors to NO. Nociception induces upregulation of cellular mechanisms, such as phosphorylated extracellular signal-regulated kinase (pERK), so dural tissues were dissected free and subjected to pERK immunohistochemistry.

The infusion of NTG promoted a delayed and robust increase in the mechanosensitivity of meningeal nociceptors, with a time course resembling the development of the delayed migraine headache. A similar sensitization was elicited by dural application of NTG and SNAP. NTG-evoked delayed meningeal nociceptor sensitization was associated with ERK phosphorylation in meningeal arteries and pharmacological blockade of meningeal ERK phosphorylation inhibited the development of NTG-evoked delayed meningeal nociceptor sensitization.

■ **COMMENTARY**

Despite extensive exploration, a detailed mechanistic explanation of migraine remains elusive. The authors concluded that development of delayed mechanical sensitization in meningeal nociceptors, evoked by the migraine trigger NTG, is potentially important as a neurophysiological correlate of migraine headache. They postulated that arterial ERK phosphorylation and its involvement in mediating the NTG-evoked delayed sensitization indicated a role of the meningeal vasculature in triggering migraine pain. However, as the authors point out, proving the importance of the meningeal vasculature in migraine pain is complicated, and intracranial meningeal vasodilatation, in isolation, may be but an intermediate step in nociceptor sensitization leading to the production of a migrainous headache. Systemic infusion of calcitonin gene-related peptide (CGRP) in migraineurs causes a delayed migrainous headache; however, CGRP is only associated with a slight vasodilatory effect. The administration of vasoactive intestinal peptide (VIP) does not trigger migraine headaches in migraineurs, despite its marked acute cephalic vasodilatatory effect. The differential effect of vasodilators in producing headache pain is perplexing, and other cerebral vasodilators should be studied to determine which can induce a delayed sensitization of meningeal nociceptors. ■

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.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter!

CME Questions

1. Features of post-radiation lower motor neuron disease may include:
   a. slowly progressive leg weakness in a patient with prior distal spinal cord and cauda equina radiation.
   b. fasciculations, muscle atrophy, and depressed or absent deep tendon reflexes.
   c. nerve conduction studies demonstrating low motor amplitudes with normal sensory responses.
   d. elevated cerebrospinal fluid protein with no cells.
   e. All the above

2. Which of the following factors best predicts which children with isolated optic neuritis will develop multiple sclerosis?
   a. Type of optic neuritis (unilateral, bilateral, or recurrent)
   b. Visual evoked potential at onset of optic neuritis
   c. Abnormal brain MRI at onset of optic neuritis
   d. Oligoclonal bands at onset of optic neuritis
   e. Both C and D

3. Which of the following is *true* about diffusion-tensor MRI (DTI)?
   a. DTI is more sensitive than conventional MRI in identifying neuropathology.
   b. DTI can diagnose Alzheimer's disease.
   c. DTI is a reliable diagnostic tool for neurodegenerative disorders.
   d. DTI is a specific test for corticobasal ganglionic degeneration.

4. Restless legs syndrome during pregnancy can be safely treated with levodopa.
   a. True
   b. False

5. Restless legs syndrome is related to:
   a. Parkinson's disease.
   b. diabetes mellitus.
   c. peripheral neuropathy.
   d. iron-deficiency anemia.
   e. All of the above

6. Which of the following statements is *true*?
   a. The migraine-like headache induced by nitric oxide occurs within minutes of administration.
   b. Meningeal vasodilatation is the main mediator of migraine headache pain.
   c. Vasoactive intestinal peptide triggers migraine headache in migraineurs through an acute cephalic vasodilatation.
   d. The initial meningeal vascular response to NTG may trigger a delayed sensitization of meningeal nociceptors.

7. Recanalization of basilar artery occlusion may be beneficial up to 48 hours after onset of symptoms.
   a. True
   b. False

8. Impairment of affective empathy is not a manifestation of stroke and suggests a psychiatric disorder.
   a. True
   b. False

In Future Issues:

Central Mechanisms for Pain Perception

Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

VOLUME 18, NUMBER 9 PAGES 17-18 SEPTEMBER 2013

Once-daily Tadalafil for ED: Efficacy and Safety

Source: Seftel AD, et al. *Int J Impot Res* 2013;25:91-98.

THE UTILIZATION OF PDE5 INHIBITION (PDE5-i) for restoration of sexual function in men suffering erectile dysfunction (ED) is well established, beginning with the introduction of sildenafil (Viagra) in 1998. In the earliest years of PDE5-i treatment, regimens were typically targeted to PRN use. Almost a decade later, consideration of lower-dose, daily use of tadalafil became popular.

In this retrospective analysis, Seftel et al report on the safety and efficacy of once-daily tadalafil (TAD-QD) in doses ranging from 2.5-10.0 mg/day. The rationale for their study was to specifically define whether age impacts the efficacy of TAD-QD, since older men (age > 50 years, by their definition) might be more refractory to PDE5-i than younger men (age < 50 years). Additionally, they wished to examine the tolerability profile of TAD-QD in men with mild-moderate ED, who comprise the largest segment of men taking PDE5-i. The dataset used in this analysis included 522 men, predominantly Caucasian (> 75%), most of whom had long-standing ED and about half of whom had comorbidities of hypertension and/or diabetes.

TAD-QD more than doubled the rates of successful intercourse (from 33.4% pretreatment to 76.8% on treatment), with no discernible difference in younger men vs older men. TAD-QD was also well tolerated, with the most common adverse events — headache, dyspepsia, and myalgias — consistent with what has been seen in prior literature.

The authors conclude that TAD-QD provides substantial improvements in ED, independent of age, in men with mild-moderate ED, and is well tolerated. ■

Psychological Disorders: How to Give Patients What They Want and What They Need

Source: McHugh RK, et al. *J Clin Psych* 2013;74:595-602.

COMMONPLACE PSYCHIATRIC DISORDERS such as anxiety, depression, post-traumatic stress disorder, and obsessive compulsive disorder respond to pharmacotherapy, psychotherapy, and their combination. The National Comorbidity Survey Replication data have indicated that persons with psychiatric disorders often do not use mental health services because of perceived barriers to access (e.g., cost, logistics). Identification of patient preferences for treatment is of value not only for patient satisfaction, but also because clinical outcomes are better among patients who receive their treatment of choice. Additionally, patients who are concordant with the therapeutic choice have been reported to be more adherent with therapy.

Data from 34 clinical trials (total patient n = 90,071) were assessed by meta-analysis. Overall, patients expressed a preference for psychological treatment over pharmacotherapy by 3:1. This preference was consistent irrespective of the underlying psychiatric disorder studied, including depression, anxiety, and hypochondriasis. The availability of additional alternatives (e.g., combination treatment, watchful waiting, no treatment) did not affect the balance of patient preferences.

At the current time, treatment of patients with mild-moderate psychiatric disorders with pharmacotherapy vs psychotherapy is at equipoise. Hence, identification of patient preference — in situations where outcomes are similar between choices — is a sensible direction to take. This large literature base suggests that as many as 75% of patients with commonplace psychiatric issues prefer psychological treatment to pharmacotherapy. Although pharmacotherapy is often a more expedient path for primary care clinicians, the importance of addressing patient preference is well highlighted by this study. ■

Reducing Stroke Risk After TIA or Minor Ischemic Stroke

Source: Wang Y, et al. *N Engl J Med* 2013;369:11-19.

THE VERY LARGE CLOPIDOGREL FOR HIGH Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) clinical trial concluded that dual antiplatelet therapy in stable ambulatory vasculopathic patients who are distant — at least 1 year post-MI, post-stroke — from their vascular event does not meaningfully reduce risk over monotherapy, and is associated with increased risk of bleeding. As convincing as this dataset is, it only addresses populations who are distant from their vascular event, rather

than subjects who are in the higher risk period immediately following an acute event.

The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial enrolled — within 24 hours of onset — Chinese subjects (n = 5170) who had sustained a minor ischemic stroke or transient ischemic attack (TIA). Subjects were randomized to treatment (double-blind) with low-dose aspirin (75 mg/d-300 mg/d) plus clopidogrel (300 mg on day 1, then 75 mg/d [CLO + ASA]) or low-dose aspirin plus placebo (ASA). The primary outcome was incidence of stroke (ischemic or hemorrhagic) over 90 days of follow-up.

CLO + ASA was associated with a 32% reduction in risk for stroke compared to aspirin alone. Risk for central nervous system hemorrhage was no different in the CLO + ASA group than ASA alone. In the immediate post-TIA/minor stroke period (up to 90 days), dual antiplatelet treatment meaningfully reduced risk without increasing bleeding. ■

Long-term Mortality Among Adults with Asthma

Source: Ali Z, et al. *Chest* 2013;143: 1649-1655.

In the United States, approximately 5000 persons die each year from asthma. Counterintuitively, deaths in asthma are equally distributed among patients identified as mild, moderate, and severe. Studies of patients with near-fatal asthma have found a decreased sensitivity to hypoxia, hypercapnea, and resistance loading, suggesting that persons destined to succumb to asthma may not fully appreciate the severity of their symptoms, placing them at risk for unrecognized deterioration.

The long-term picture of causes of death in asthmatic adults was the subject of this report by Ali et al. The authors drew on a population of asthmatics enrolled from 1974-1990 in Denmark at their first visit for asthma to the Copenhagen Frederiksbergy Hospital Allergy and Chest Clinic, having been referred there by their general practitioners in the community. More than 75% of the enrollees were younger than 50 years of age at the time of enrollment.

Compared with age- and sex-matched control subjects, all-cause mortality in asthmatic subjects was essentially doubled over 25 years of follow-up. The excess risk for death was primarily due to obstructive airways disease, but was unrelated to smoking status (hence deaths were predominantly *not* related to chronic obstructive pulmonary disease). Degree of peripheral blood eosinophilia correlated with mortality, intimating that unmitigated atopy in asthmatics may contribute to adverse outcomes. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media, LLC.

Executive Editor: Leslie Coplin.
Editor: Stephen Brunton, MD.
Managing Editor: Neill L. Kimball.

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: neill.kimball@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305.

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

Source: The Look AHEAD Research Group. *N Engl J Med* 2013;369:145-154.

Type 2 diabetes (DM2) is characterized by increased risk for cardiovascular (CV) events, which are not only more frequent but also more severe than similar events in non-diabetics. Most DM2 patients in America are overweight or obese. Weight loss and exercise have been shown to improve glucose control, lipids, blood pressure, and progression from pre-diabetes to diabetes, but no large clinical trials have confirmed risk reduction for CV events attributable to lifestyle intervention.

The Look AHEAD trial randomized overweight or obese DM2 patients (n = 5145) to intensive lifestyle or control (the control group still received education and support in reference to care of their DM2). The goal of intensive lifestyle was to reduce weight by at least 7% and participate in at least 175 minutes/week of moderate-intensity physical activity.

The trial was originally intended to go on for 13.5 years, but was stopped early (at 9.6 years) because futility analysis demonstrated no likely possible benefit of the intensive intervention for CV events compared to controls, despite greater weight loss and improved glycemic control attained in the intensive lifestyle group.

Intensive lifestyle intervention in DM2 improves glycemic indices and body mass index, but does not appear to improve CV risk. ■

New Hope for Hepatitis C Patients

Source: Jacobson IM, et al. *N Engl J Med* 2013;368:1867-1877.

The Centers for Disease Control and Prevention has recently advocated routine screening for hepatitis C (HEP-C) among all adults born from 1945-1965. These recommendations stem from the observation of the ever-growing burden of persons with HEP-C and its consequences who do not necessarily endorse traditionally recognized risk factors for HEP-C such as intravenous drug use, tattoos, etc. Early identification allows for potential cure of HEP-C, since as many as 80% of previously untreated individuals can achieve sustained virologic response with "standard" antiviral regimens (e.g., ribaviron plus interferon).

This does, however, leave a substantial minority of HEP-C patients (those who fail treatment, who are intolerant of treatment, or who have contraindications to it) at risk. Fortunately sofosbuvir, a new polymerase inhibitor, has demonstrated high efficacy in both untreated HEP-C and treatment failures.

Sofosbuvir was studied in two populations of HEP-C genotype 2 or 3: persons with contraindications to interferon and cases that had not responded to interferon therapy. Sustained virologic response was seen in 78% of subjects with interferon contraindications, and (at 16 weeks) 73% of interferon failures. Sofosbuvir was generally well tolerated, with a discontinuation rate of 1-2%. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Do Statins Prevent Parkinson's Disease?

In this issue: Statins and Parkinson's disease; safety and tolerability of statins; apixaban and venous thromboembolism; and FDA actions.

Statins and Parkinson's disease

In 2012, the FDA expanded warnings on statins to include cognitive impairment, such as memory loss, forgetfulness, and confusion, based on adverse event reports from some statin users. There have been few data to confirm cognitive changes or other neurologic side effects associated with these drugs other than case reports. But still, many media outlets have reported that this warning is evidence of increased risk for Alzheimer's disease and other brain disorders. To the contrary, in last year's warning, the FDA specifically stated that memory changes are reversible when the medication is stopped. Other studies have suggested that highly lipophilic statins such as simvastatin, which crosses the blood-brain barrier easily, may in fact protect against dementia — although other studies refute this finding. Parkinson's disease (PD) has also been studied with regard to statin therapy, and those data may be a bit more compelling in favor of statins. A recent study from Taiwan took a unique approach to this problem. Reasearchers looked at the incidence of PD in patients who discontinued statin therapy compared to those who continued. Among the nearly 44,000 statin initiators, the incident rate for PD was 1.68 per 1.000,000 among lipophilic statin users and 3.52 among hydrophilic statin users. Continuation of lipophilic statins was associated with a marked decrease in the risk of PD compared to discontinuation (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.27-0.64]). This finding was not affected by comorbidities or other medications. Hydrophilic statins did not reduce the occurrence of PD. Among the lipophilic statins, simvastatin had the greatest effect (HR, 0.23; 95% CI, 0.07-0.73), while atorvastatin was also beneficial (HR, 0.33; 95% CI, 0.17-0.65). The effect among women was even more dramatic with a nearly 90% reduction in the incidence of PD for simvastatin and a 76% reduction for atorvastatin. Most of the benefit was seen in the elderly subgroup. The authors suggest that continuation of a lipophilic statin was associated with a decrease in the incidence of PD as compared to discontinuation, especially in women and the elderly (*Neurology* published online July 24, 2013. DOI: 10.1212/WNL.0b013e31829d873c). An accompanying editorial suggests that the lipophilic statins may reduce oxidative stress, and may have other direct actions in the brain that reduce the risk of PD, although more research is needed. The authors add, "For those who have to be on statins, it is a comforting thought that there is potential added advantage of having a lower risk of PD, and possibly other neurologic disorders as well." (*Neurology* DOI: 10.1212/WNL.0b013e31829d87bb). ■

Safety and tolerability of statins

Overall statin safety and tolerability was the focus of a recent (non-company sponsored) meta-analyses of more than 135 trials involving nearly 250,000 individuals. Statin therapy was no differ-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

ent from control with regard to myalgia, creatine kinase elevation, cancer, or discontinuation due to adverse events. There was a higher incidence of diabetes associated with statin use (odds ratio [OR], 1.09; 95% CI, 1.02-1.16). Transaminases were also elevated more commonly (OR, 1.51; 95% CI, 1.24-1.84). The safest statins appeared to be simvastatin and pravastatin. When similar doses were compared, there were higher discontinuation rates with atorvastatin and rosuvastatin. The highest dose (80 mg) of simvastatin was associated with a significantly increased risk of creatine kinase elevation (OR, 4.14; 95% CI, 1.08-16.24). The authors conclude that statins, as a class, are well tolerated, except for a higher risk of diabetes. Simvastatin and pravastatin seem to be more tolerable than other statins (*Circ Cardiovasc Qual Outcomes* published online July 9, 2013. DOI: 10.1161/CIRCOUTCOMES.111.000071). ■

AMPLIFY trial results

Currently, there are three novel oral anticoagulants on the market — dabigatran, rivaroxaban, and apixaban. All are approved for stroke prevention in patients with nonvalvular atrial fibrillation, but only rivaroxaban is approved for deep vein thrombosis/pulmonary embolism (PE) prevention and treatment. That may change with the publication of the AMPLIFY trial, which compared apixaban with conventional anticoagulant therapy in patients with acute venous thromboembolism (VTE). In a randomized, double-blind study, apixaban was compared with enoxaparin/warfarin (conventional therapy) in nearly 5400 patients with acute VTE. The primary outcome was recurrent symptomatic VTE or death related to VTE. The principal safety outcomes were major bleeding alone and major bleeding plus clinically relevant nonmajor bleeding. The primary outcome (recurrent VTE) occurred in 59 of 2609 patients (2.3%) in the apixaban group compared with 71 of 2635 (2.7%) in the conventional therapy group (relative risk [RR] 0.84; 95% CI, 0.60-1.18). Major bleeding occurred in 0.6% of those in the apixaban group and 1.8% in the conventional therapy group (RR, 0.31; 95% CI, 0.17-0.55; $P < 0.001$ for superiority). The composite outcome of major bleeding and nonmajor bleeding occurred more than twice as often in the conventional therapy group. Rates of adverse events were similar. The authors conclude that a fixed-dose regimen of apixaban alone was noninferior to conventional therapy for the treatment of acute VTE and was associated with less bleeding. The findings were the same for patients with PE or extensive disease (*N Engl J Med* published online July 1, 2013. DOI: 10.1056/NEJMoa1302507). An accompanying editorial states that this is "an exciting time in thrombosis care," although more information is needed on reversal strategies and monitoring of these new agents (*N Engl J Med* July 1, 2013. DOI: 10.1056/NEJMe1307413). The option to safely treat VTE with fixed-dose oral options is very appealing. Both dabigatran and apixaban are expected to be reviewed for these indications in the near future. ■

FDA actions

The FDA has issued a Safety Communication regarding the oral antifungal ketoconazole that includes limiting the drug's use. The warning states that ketoconazole should never be used as a first-line agent due to the risk of liver toxicity, adrenal insufficiency, and drug interactions. The new guidance states that ketoconazole should only be used "when alternative antifungal therapies are not available or tolerated." In addition, the agency has revised the list of indications for the drug, removing dermatophyte and *Candida* infections.

The FDA has also issued a Safety Communication about the antimalarial drug mefloquine hydrochloride regarding neurologic and psychiatric side effects. The drug is used for treatment of malaria but more commonly for prevention of *Plasmodium falciparum* (including chloroquine-resistant *P. falciparum*) and *P. vivax*. Neurologic side effects — which may be permanent — include dizziness, loss of balance, and tinnitus. Psychiatric side effects include anxiety, paranoia, depression, or hallucinations. The brand form of mefloquine (known as Lariam) is no longer marketed, but several generic forms of the drug are available. The new warnings are contained in a boxed warning — the FDA's most serious warning. The drug was recently in the news regarding a number of violent military incidents among soldiers taking the drug, including the murder of 16 Afghan civilians last year.

A nasal steroid spray may soon be available over the counter (OTC). The FDA's Nonprescription Drugs Advisory Committee has recommended the switch to OTC for Sanofi's triamcinolone acetonide (Nasacort AQ), the popular steroid nasal spray for the treatment of seasonal and perennial allergic rhinitis. The drug was originally approved in 1996 for use in adults and children ages 2 years and older, and has been widely used since. If approved by the full FDA later this year, it would be the first nasal steroid to be sold OTC. The drug has been available as a generic since 2008. ■