Providing Evidence-based Clinical Information for 27 Years

NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

INSIDE

Financial Disclosure:

Neurology Alert's physician editor, Matthew Fink, MD, reports no consultant, stockholder, speaker's bureau, research, or other relationships related to this field of study. Peer reviewer M. Flint Beal, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company having ties to this field of study.

Painful Legs and Moving Toes: How to Diagnose and What to Do?

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD

Assistant Professor, Department of Neurology and Neuroscience, Weill Medical College, Cornell University

Dr. Henchcliffe serves on the speaker's bureau for GlaxoSmithKline, Teva, Boehringer Ingelheim, Schwarz Pharma, and Allergan.

Synopsis: *Fourteen cases of the rare and difficult to treat "painful legs and moving toes" syndrome are presented. The cases included diverse etiologies—polyneuropathy, radiculopathy, or neuroleptic use—and half responded to GABAergic medications.*

Source: Alvarez MV, et al. Case series of painful legs and moving toes: Clinical and electrophysiologic observations. *Mov Disord* 2008;23:2062-2066.

PAINFUL LEGS AND MOVING TOES (PLMT) IS A RARE SYNDROME OF pain in the legs and feet, usually preceding involuntary movements in the feet or toes. The authors of this report reviewed 4780 patients diagnosed with a movement disorder at the Mayo Clinic in Arizona from 1996-2006, and identified 14 cases of PLMT and its variants (age range, 25-84 years; mean, 69 years). Eight patients had "classic" PLMT, 2 had PLMT with painful hands and moving fingers (PHMF), 2 had painless legs and moving toes (P-LMT), and 2 had PLMT with painless hands and moving fingers (P-HMF).

Most patients sought evaluation specifically for pain, which was described mostly as burning, but also as numbness, shooting, aching, or dull. Limb movements included flexion-extension, fanning, clawing, and abduction-adduction, usually asymmetric, asynchronous, and partially suppressible. In one patient observed at night, the movements continued into light sleep (stages N1 and N2). Notably, 11 patients had clinical evidence of peripheral neuropathy, thought to be associated with lumbar stenosis (n = 3), Sjogren syndrome (n = 3), diabetes (n = 2), and 1 each with IgG polyclonal gammopathy, vitamin B_{12} deficiency, lupus erythematosus, and no known cause.

VOLUME 27 • NUMBER 4 • DECEMBER 2008 • PAGES 25-32

NOW AVAILABLE ONLINE
www.ahcmedia.com

Seven patients responded to either pregabalin (75-1500 mg daily) or gabapentin (300-2400 mg daily), but in the remainder no drug treatment was effective. Of the 3 cases without neuropathy, 1 had no discernable cause, but 2 were associated with neuroleptic use (ziprasidone, perphenazine), and each responded to stopping or switching the medication. Seven patients underwent surface electromyography to better characterize their movements. Random irregular bursts of activity or semicontinuous bursts were observed (80-1000 msec), sometimes with a semi-rhythmic pattern (0.5-1 Hz) and sometimes with co-contraction of antagonists and neighboring muscles (i.e., features of chorea and dystonia).

■ COMMENTARY

PLMT is a rare movement disorder that is little known and poorly understood. Apart from one previous case series from the United Kingdom, descriptions have been limited to isolated case reports, so this study represents a significant addition to our body of knowledge. At face value, it should be a clear-cut diagnosis, but it is likely that in practice, some are misdiagnosed. If the involuntary movements are not observed, isolated pain or discomfort could easily be interpreted as peripheral neuropathy alone. Unexplained sensations coupled with a movement disorder could also be misdiagnosed as restless legs syndrome (RLS): It is therefore important to elicit any diurnal rhythm (RLS is almost always worse at night) and precipitants (RLS worsens with inactivity), and to observe the movements directly. The appearance and timing of periodic limb movements of sleep associated with the majority of RLS cases are unlike those of PLMT. A diagnosis of PLMT should then stimulate a search for its etiology. Since cases associated with peripheral neuropathy were overwhelmingly associated with underlying causes, including vitamin B_{12} deficiency, diabetes mellitus, and autoimmune disease in this series, a low threshold should be maintained for obtaining nerve conduction studies in anyone suspected of suffering from PLMT.

One interesting point raised in this study is that 2 cases were associated with neuroleptic use (as has been previously reported). The authors make a convincing point that neuroleptic-induced PLMT is distinct from tardive dyskinesia because of the associated pain (unusual in choreiform tardive syndromes) and location (unusual for tardive dyskinesias to be present in the toes). However, the relationship between these syndromes remains to be fully determined.

Finally, PLMT has traditionally been extremely challenging to treat. However, since half of the cases with neuropathy-associated PLMT responded either to pregabalin or gabapentin, these would appear to be the drugs of choice for first-line treatment. ■

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

ASSOCIATE PUBLISHER: Coles McKagen.
SENIOR MANAGING EDITOR: Paula Cousins
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 740059,
Atlanta, GA 30374.

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 Address:
customerservice@ahcmedia.com
Editorial E-Mail Address: paula.cousins@ahcmedia.com
World-Wide Web: www.ahcmedia.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $319
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 LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of *25 AMA PRA Category 1 Credits™*. Physicians should only claim 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 LLC

Questions & Comments
Please call **Paula Cousins**, Senior Managing Editor, at (404) 262-5468.

IV Valproic Acid vs Phenytoin: Old Standby or the New Challenger?

ABSTRACT & COMMENTARY

By Padmaja Kandula, MD

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

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

Synopsis: *Valproic acid and phenytoin were equally effective in the treatment of acute repetitive seizures and status epilepticus.*

Source: Gilad R, et al. Treatment of status epilepticus and acute repetitive seizures with i. v. valproic acid vs phenytoin. *Acta Neurol Scand* 2008;118:296-300.

HISTORICALLY, THE BENZODIAZEPINES AND PHENYTOIN have been used as first-line therapy in aborting status epilepticus (SE). The rationale for use of these two agents mainly rests on the 1998 results of the Veterans

Affairs Cooperative Trial. The greatest response rate was seen in those patients who received benzodiazepines in addition to phenytoin (PHT), rather than PHT alone. Although the intravenous formulation of valproic acid (VPA) was officially approved by the FDA in 1996, the agent was not included in the Veterans Affairs Cooperative Trial and still has not received approval by the FDA for use in SE. Nevertheless, despite the lack of FDA approval, IV VPA continues to be used off-label by clinicians. Therefore, papers such as this one by Gilad et al are critical in defining the exact role of VPA in both acute repetitive seizures (ARS) and SE.

Seventy-four adult patients with either ARS or SE older than age 18 were included in this open-label study. Patients with baseline abnormal liver function tests or previous toxic serum levels of VPA were excluded from the study. For this study, SE was defined as greater than 30 minutes of continuous seizure activity or two or more sequential seizures without clinical recovery. ARS was defined as two or more repetitive seizures with clinical recovery between seizures during a 5- to 6-hour period. The primary endpoint was cessation of clinical seizure activity within 20 minutes of either VPA or PHT infusion, without rescue medication intervention. The secondary endpoint was assessment of infusion tolerability over the subsequent 24 hours.

The IV VPA patient group received 30 mg/kg given over 20 minutes. The PHT patient group received an infusion of 18 mg/kg also given over 20 minutes. Patients were treated randomly in the emergency room in a 2:1 ratio of either VPA or PHT infusion. If seizure control was not achieved by infusion of the first study drug, then patients were treated with the other study drug. Patients who failed both study drug infusions were then treated with IV midazolam at a dosage of 0.2 mg/kg and were then subsequently transferred to the intensive care unit. Electroencephalography was performed in select cases of clinically suspected nonconvulsive status where patients did not regain consciousness.

Forty-nine patients were treated with IV VPA and 25 patients were treated with PHT. Nearly two-thirds of patients in the study experienced breakthrough seizures secondary to subtherapeutic anti-epileptic drug levels or non-compliance. Post-stroke epilepsy made up approximately 25% of patients. Twelve percent of both the IV VPA and IV PHT groups required rescue medication. No significant side effects were found in the VPA group. One patient in the PHT group (no prior cardiac history) experienced ventricular premature beats during the infusion, one experienced vertigo, and one was noted to develop hyponatremia.

■ COMMENTARY

In this study, IV VPA treatment was as efficacious as IV PHT treatment as first-line treatment for ARS and SE. Other studies have also documented the efficacy of IV VPA; however, lack of uniformity in loading doses of IV VPA and rate of infusion make any definite conclusions about VPA in acute treatment of seizures difficult. Although this particular study was prospective, the open-label nature of the study introduces potential bias. Also, more than two-thirds of the patients were acute repetitive patients, rather than patients in SE, potentially influencing an overall better outcome for either PHT or VPA infusion.

Despite the above design flaws, the authors present some compelling evidence for the use of VPA. This study and others have shown good tolerability of IV VPA. In our center, IV VPA has been used as a second-line (in cases of phenytoin allergy) or third-line agent in the treatment of SE, before the use of phenobarbital, particularly in patients in whom intubation is not being considered. Multiple studies have shown good tolerability of IV VPA at a rate of 6 mg/kg/min.[1-6] Theoretically, with an infusion rate of 6 mg/kg/min and dosage of 25-30 mg/kg, in an average 70 kg individual, IV VPA can be administered in approximately 5 minutes. There are also particular instances where VPA would be the agent of choice in aborting status, such as absence status epilepticus.

As awareness of SE grows, more prompt treatment of this neurologic emergency will hopefully result in less need to proceed to anesthetic agents. Valproic acid, with its relatively rapid onset of action and minimal side effects, may evolve into an attractive choice in the treatment of SE and ARS. ■

References

1. Ramsay RE, et al. Safety and tolerance of rapidly infused Depacon. A randomized trial in subjects with epilepsy. *Epilepsy Res* 2003;52:189-201.
2. Sinha S, Naritoku DK. Intravenous valproate is well tolerated in unstable patients with status epilepticus. *Neurology* 2000;55:722-724.
3. Venkataraman V, Wheless JW. Safety of rapid intravenous infusion of valproate loading in epilepsy patients. *Epilepsy Res* 1999;35:147-153.
4. Wheless J, Venkataraman V. Safety of high intravenous valproate loading doses in epilepsy patients. *J Epilepsy* 1998;11:319-324.
5. Naritoku DK, Mueed S. Intravenous loading of valproate for epilepsy. *Clin Neuropharmacol* 1999;22:102-106.
6. Wheless JW, et al. Rapid infusion with valproate sodium is well tolerated in patients with epilepsy. *Neurology* 2004;63:1507-1508.

Carotid Arterial Dissection: Time for a Randomized Clinical Trial

ABSTRACT & COMMENTARY

By John J. Caronna, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *There are no randomized controlled treatment trials of cervical artery dissection, and the most effective therapy is uncertain.*

Source: Menon R, et al. Treatment of cervical artery dissection: A systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2008;79:1122-1127.

CEREBRAL ARTERIAL DISSECTION IS AN IMPORTANT cause of stroke, especially in the young. Potential stroke mechanisms include both hemodynamic compromise and embolism. Evidence from cerebral angiography and transcranial Doppler studies suggests that embolism is the more important cause of stroke.[1] Natural history data indicate a high risk of early recurrent stroke, largely within the first month after onset.[2]

Menon et al performed a systematic review and a meta-analysis to determine the effectiveness of the different treatment approaches to carotid arterial dissection. They performed separate searches and reviews of: 1) antiplatelet and anticoagulant drugs, 2) thrombolysis, and 3) angioplasty with stenting. For each they searched Medline and PubMed from 1966 to April 2007.

There were sufficient data for meta-analysis, only to compare antiplatelet treatment with anticoagulation. No randomized controlled trial (RCT) was found. In 34 non-randomized studies comprising 762 patients there was no significant difference in the risk of stroke or death. There were four non-randomized studies of thrombolysis that provided insufficient data to assess efficacy. Complication rates were not greater than in thrombolysis for other causes of ischemic stroke.

Six studies comprised 96 patients who underwent stenting for both acute dissection and its chronic complications (stenosis and dissecting aneurysm). Data were insufficient for assessment of efficacy. Complication rates were similar to those published for stenting in atherosclerotic carotid stenosis.

The authors concluded that no data support the therapeutic superiority of anticoagulants over antiplatelet agents. Thrombolysis and stenting appear safe but conclusions about efficacy require more data.

■ COMMENTARY

Like many other medical and surgical interventions intended to cure disease or prevent disability, the commonly used treatments for cervical artery dissection have not been subjected to rigorous testing by RCT. Observational studies from the Mayo Clinic[3] among others have suggested that antiplatelet therapy is sufficient in carotid dissection without neurological deficits apart from Horner syndrome, but that anticoagulation should be employed in carotid dissection presenting with stroke. Clinicians have used their best judgment in choosing among the available treatments for carotid dissection and remain free to do so.

The systematic review of more than 700 patients treated with antiplatelet or anticoagulant therapy provides useful information for clinicians and justifies the need for an RCT. The authors lamented that "there were no data from randomized trials and much of the data were of poor quality." The authors' failure to find even one RCT reminds me of another systematic search for RCTs of "parachute use to prevent death and major trauma related to gravitational challenge."[4] Alas, in that study, the tongue-in-cheek authors, too, could not find a single RCT of parachute use. They wisely concluded that the basis for parachute use is purely observational and its apparent efficacy potentially could be explained by bias in selection and reporting, "the healthy cohort effect." They invited those who advocate evidence-based medicine to demonstrate their commitment by volunteering for a double-blind RCT of the parachute. Any takers? ■

References

1. Srinivasan J, et al. Transcranial Doppler in the evaluation of internal carotid artery dissection. *Stroke* 1996;27:1226-1230.
2. Biousse V, et al. Time course of symptoms in extracranial carotid artery dissections. A series of 80 patients. *Stroke* 1995;26:235-239.
3. Mokri B, et al. Spontaneous dissection of the cervical internal carotid artery. *Ann Neurol* 1986;19:126-138.
4. Smith GC, Pell JJ. Parachute use to prevent death and major trauma related to gravitational challenge: Systematic review of randomised controlled trials. *BMJ* 2003; 327:1459-1461.

A Neurophysiology Study: Thalidomide and Sensory Neurotoxicity

ABSTRACT & COMMENTARY

By Norman Latov, MD, PhD

Professor of Neurology and Neuroscience, and Director of the Peripheral Neuropathy Center, Weill Medical College, Cornell University

Dr. Latov received grants/research support from Talecris Biopharmaceuticals, is a stockholder in Therapath LLC, is a retained consultant for Quest Diagnostics, and received royalty payments from Athena Diagnostics.

Synopsis: *Axonal sensory neuropathy is a common complication of thalidomide therapy and occurs at a lower than expected dose in patients with cutaneous lupus.*

Source: Zara G, et al. Thalidomide and sensory neurotoxicity: A neurophysiological study. *J Neurol Neurosurg Psychiat* 2008;79:1258-1261.

PERIPHERAL NEUROPATHY IS A COMMON, DOSE-LIMITING complication of thalidomide, which is increasingly used to treat oncological and inflammatory conditions due to its anti-angiogenic, immunomodulatory, and pro-apoptotic properties. This study investigated the development of neuropathy in a group of patients who were treated with thalidomide for cutaneous lupus erythematosus over a 6-year period.

Eleven of the 12 patients developed a reduction of sensory action potential (SAP) amplitudes in the sural nerve, but not in the upper limbs. In 9 patients, the SAP amplitude reduction was > 50%. None had slowing of nerve conduction velocities, or abnormal needle electromyography. Five developed symptoms of numbness or paresthesias in the toes and fingers, or leg cramps. Four had distal sensory loss to tactile and pain stimuli. Vibration and joint position sense, and deep tendon reflexes were unchanged, and there was no weakness or autonomic involvement. The median duration time to development of a 50% reduction in SAP amplitude was 14 months (range, 4.5-29 months), and the mean cumulative thalidomide dose was 21.4 g (range, 9.4-40 g). Four patients stopped treatment due to reduction in the SAP amplitudes, but 7 refused discontinuation because of the clinical benefits. After thalidomide was discontinued, 8 patients showed no significant improvement in the SAP amplitudes, 2 showed partial recovery, and one total recovery. Sensory symptoms partially improved, but there was no change in the sensory loss.

The authors note that thalidomide causes a length-dependent distal axonal neuropathy, without involvement of motor fibers or dorsal root ganglia neurons. As such, if a patient treated with thalidomide develops a syndrome resembling sensory neuronopathy, multifocal or motor neuropathy, or demyelination, then other causes for the neuropathy, possibly related to the underlying disease for which the thalidomide is given, should be considered.

■ COMMENTARY

A previous study indicated that the threshold cumulative dose required for development of thalidomide neurotoxicity was greater than 20 g,[1] which is considerably higher than that reported in the current study. A confounding factor, however, is that many patients with lupus have a mild underlying neuropathy which might make them more susceptible to thalidomide neurotoxicity. Neuropathy is a major dose-limiting complication in patients treated with thalidomide for myeloma, where doses of greater than 150 mg/day are commonly employed.

Patients taking thalidomide or other potentially neurotoxic agents are rarely evaluated for neuropathy unless they become symptomatic. The current study, however, shows that these drugs can cause significant and irreversible nerve damage without overt symptoms or signs. As such, patients should be examined prospectively for development of neurotoxicity, both clinically or using electrodiagnostic studies or possibly determination of epidermal nerve fiber density by skin biopsy, even in the absence of neuropathic symptoms.

There is a general reluctance on the part of both physicians and patients that use neurotoxic agents to report the development of neuropathy, as that would limit the effective therapy. That reluctance, however, is in part responsible for the relative lack of research into the mechanisms of neurotoxicity, or the development of agents that would prevent the neuropathy. An example of a successful therapeutic intervention is the use of vitamin B_6 to prevent the development of neuropathy in patients taking isoniazid for tuberculosis, based on our understanding of the metabolic effects of isoniazid. ■

Reference

1. Goransson LG, et al. Small-diameter nerve fiber neuropathy in systemic lupus erythematosus. *Arch Neurol* 2006;63:401-404.

Needle Electromyography: Hemorrhagic Risks and Complications

ABSTRACT & COMMENTARY

By Michael Rubin, MD, FRCP(C)

Professor of Clinical Neurology, Weill Cornell Medical College, New York, NY

Dr. Rubin receives grant/research support from Pfizer and is on the speaker's bureau of Athena Diagnostics.

Synopsis: *Needle EMG is a safe procedure in patients who are taking antiplatelet or warfarin therapy.*

Source: Lynch SL et al. Complications of needle electromyography: Hematoma risk and correlation with anticoagulation and antiplatelet therapy. *Muscle Nerve* 2008;38:1225-1230.

Is there an increased risk of hematoma formation following needle electromyography (EMG) in patients on aspirin, clopidogrel, or warfarin? To address this question, adult patients undergoing EMG of the tibialis anterior muscle, as part of a routine lower extremity EMG, were enrolled in a prospective, case-control study undertaken at the Mayo Clinic Electromyography Laboratory. Post-EMG ultrasound examination of the tibialis anterior muscle was central to the study design, and hence, embedded metal in proximity to the tibialis anterior was criteria for exclusion. Participating patients completed a questionnaire addressing medication use, including herbal supplements and potential blood thinners. Following needle EMG of the tibialis anterior muscle, ultrasound of the muscle was performed to ascertain the presence and size of hematoma, if any. Needle EMG was performed by a supervised resident, fellow, or attending, following standard technique, using a concentric 50 mm needle directed in a straight line along 3 different tracks, following which the needle was removed and firm pressure applied to achieve hemostasis. Informed consent and HIPAA authorization were obtained in all instances. Fisher's exact test provided statistical analysis.

Among 209 enrolled patients, 101 were on warfarin with an INR > 1.4 (range, 1.5-4.2), 57 were on antiplatelet agents (aspirin, clopidogrel, or both), and 51 served as control subjects. Among the warfarin patients, 80 had an INR of 2.0 or more and 27 had an INR of 3.0 or more. No control patient had ultrasound evidence of hematoma, and only 1 aspirin/clopidogrel patient and 2 warfarin patients had subclinical hematoma. No statistically significant difference was appreciated between the groups. All hematomas were asymptomatic, with no evidence of bruising or swelling at the needle entry site following the study. Long-term follow-up of medical records at 3-15 months similarly reported no complaints of pain following the EMG. Needle EMG rarely causes hematoma formation. It may be safely performed even in patients on warfarin with INR in the therapeutic range.

■ COMMENTARY

Patients with lymphedema or prosthetic joints represent two other situations in which the safety of needle EMG is brought into question. Lymphedema may follow lymph node dissection or radiation, and patients are often cautioned to avoid any percutaneous procedure in the affected limb, including venipuncture due to the risk of infection. Prosthetic joints may become infected due to hematogenous spread of bacteria as may occur following dental procedures or gastrointestinal studies, and possibly needle EMG. Guidelines issued by the American Association of Neuromuscular and Electrodiagnostic Medicine state that, based on the medical literature, no contraindication to needle EMG exists in either of these conditions.[1] Nevertheless, clinical judgment should be exercised to determine whether the information to be obtained outweighs the risk of complication. ■

Reference

1. American Association of Neuromuscular and Electrodiagnostic Medicine. Needle EMG in certain uncommon clinical contexts. *Muscle Nerve* 2005;31:398-399.

Anxiety in Parkinson's Disease: Diagnostic Evaluation and Pitfalls

ABSTRACT & COMMENTARY

By Melissa J. Nirenberg, MD, PhD

Assistant Professor, Neurology and Neuroscience, Weill Cornell Medical College

Dr. Nirenberg has consulted for Biovail and participated in clinical trials sponsored by Boehringer-Ingelheim.

Synopsis: *Anxiety is a common but underrecognized symptom of Parkinson's disease, for which there are a number of suggested but no recommended rating scales.*

Source: Leentjens AF, et al. Anxiety rating scales in Parkinson's disease: Critique and recommendations. *Mov Disord* 2008;23:2015-2025.

THE EVALUATION AND TREATMENT OF PARKINSON'S DISease (PD) is mainly focused on the well-recognized motor features of the disease, such as rest tremor, rigidity, and bradykinesia. In recent years, however, there has been increasing recognition of the high prevalence and major clinical impact of the non-motor symptoms of PD. Anxiety is one of the most common and treatable of these non-motor symptoms, and yet one about which there has been surprisingly little clinical research.

One of the major impediments to the study of anxiety in PD has been the lack of recommended PD anxiety rating scales. To address this problem, a task force was commissioned by the Movement Disorder Society to systematically evaluate the clinimetric properties of anxiety rating scales that had been previously validated or used in peer-reviewed publications about PD. Based on a literature search, the authors identified and evaluated 6 of these scales. These included the Beck anxiety inventory (BAI), hospital anxiety and depression scale (HADS), Zung self-rating anxiety scale (SAS) and anxiety status inventory (ASI), Spielberger state trait anxiety inventory (STAI), and Hamilton anxiety rating scale (HARS). They also examined item 5 (anxiety) on the neuropsychiatric inventory (NPI) because of the frequency with which it has been used in PD; other multidimensional scales were excluded. Each rating scale was critically reviewed by two task force members. Rating scales were then classified as "recommended" (used in PD beyond the original developers, with successful clinimetric testing), "suggested" (used in PD beyond the original developers or used in PD with successful clinimetric testing in this population), or "listed" (used in PD only by the original developers, with no successful clinimetric testing in PD).

A brief summary of their findings was presented in the printed version of the journal article, with greater detail presented in the accompanying on-line version. The BAI was "suggested" as a screening test for episodic anxiety disorders (such as panic attacks), for studying the epidemiology and biomarkers of anxiety symptoms, and for evaluating responses to changes in treatment. The HADS had limited clinimetric information, and was therefore "suggested" for use in screening for anxiety, but not for studying the phenomenology of anxiety disorders in PD. The Zung SAS had been used in epidemiological studies in PD, but not validated in this population, and the ASI has only been used in one study in PD; neither has been used in PD treatment studies. These studies were therefore also classified as "suggested" for use in PD. The STAI has not been validated in PD, but was found to be particularly useful for evaluating sustained anxiety disorders such as generalized anxiety disorder, and was "suggested" for use in screening for anxiety, studying anxiety biomarkers, and as an outcome measure in PD. The HARS has not been validated in PD, nor is there any information about its clinimetric properties in PD, but it has been used in studies of the epidemiology and symptomatology of anxiety in PD patients and, therefore, met criteria as "suggested" for use in PD. The NPI anxiety subscale also had almost no data about its clinimetric properties in PD, but was "suggested" for use in PD, and may be most useful as a screening tool for anxiety, or for estimating the severity of anxiety in patients with dementia.

In the final analysis, the task force classified all of the above anxiety rating scales as "suggested" and none of them as "recommended" for use in PD. This was because none of the rating scales had undergone successful clinimetric testing and in PD. The task force concluded that further study was needed before any of these rating scales could be specifically recommended for use in PD, and that if none of these scales prove to be acceptable, then it may be necessary to devise a new PD-specific anxiety rating scale.

■ COMMENTARY

Anxiety has been associated with reduced quality of life and greater subjective motor symptoms in PD, and with increased caregiver burden and health care utilization in the general population. Yet remarkably little is known about the prevalence, prognosis, and treatment in PD. Rating scales that accurately identify and quantify the severity of anxiety in PD are needed to support clinical research about the prevalence and optimal treatments of anxiety in PD, and to facilitate accurate clinical diagnosis in the setting of routine patient care.

The clinical presentation of anxiety in PD appears to differ from that in the general population, such that standard anxiety rating scales—and even the "gold standard" DSM-IV criteria—may misclassify patients. Anxiety symptoms (such as shakiness, restlessness, and dizziness) may have considerable overlap with symptoms of depression, motor features of PD (such as tremor and akathisia), and other non-motor PD symptoms (such as dizziness due to orthostatic hypotension). PD patients may also experience fluctuations in anxiety related to medication timing ("non-motor offs"), and medication-induced impulse-control disorders. These unique properties of anxiety in PD underscore the importance of identifying rating scales that appropriately

identify and measure the severity of anxiety in PD.

This report supports the use of a number of different rating scales that can be used in PD, provides useful information about the strengths and weaknesses of the various tests that are available, and highlights the need for further study before any specific scale can be classified as "recommended." More importantly, the report calls attention to the need for greater research about this common, debilitating, and treatable non-motor manifestation of PD. ■

CME Questions

16. Painful legs and moving toes syndrome is associated with:
a. an urge to move the limbs with relief after movement.
b. an excellent response to dopamine agonists.
c. peripheral neuropathy in some.
d. worsening at night.
e. face and tongue chorea.

17. Phenytoin is more effective than valproic acid (VPA) in the treatment of acute seizures.
a. True
b. False

18. Intravenous VPA causes more side effects than IV phenytoin.
a. True
b. False

19. Data from randomized clinical trials in carotid dissection patients have proven the efficacy of:
a. aspirin.
b. warfarin.
c. IV tPA.
d. angioplasty with stenting.
e. None of the above

20. Which of the following statements about thalidomide therapy is *true*?
a. Numbness and tingling in the feet are common.
b. Sensory action potential amplitudes are reduced.
c. Cumulative dose is associated with neuropathy.
d. Spontaneous improvement may occur with cessation of treatment.
e. All of the above

21. Needle electromyography carries a significant risk of hematoma formation in patients taking:
a. aspirin.
b. clopidogrel.
c. warfarin.
d. None of the above

22. Which of the following rating scales has been validated and is officially recommended for use in Parkinson's disease?
a. Beck anxiety inventory
b. Hospital anxiety and depression scale
c. Spielberger state trait anxiety inventory
d. None of the above

Answers: 16. c, 17. b, 18. b, 19. e, 20. e, 21. d, 22. d.

CME Objectives

The objectives of *Neurology Alert* are:

• To present the current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;

• To discuss the pathogenesis and treatment of pain;

• To present basic science lessons in brain function;

• To discuss information regarding new drugs for commonly diagnosed diseases and new uses for traditional drugs;

• To discuss nonclinical issues of importance to neurologists, such as the right to die and the physician's legal obligation to patients with terminal illness. ■

CME Instructions

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

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

NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

CUMULATIVE INDEX
Volume 26, Numbers 5-12, Pages 1-96
Volume 27, Numbers 1-4, Pages 1-32
January 2008-December 2008

Please note, Volume listed first, then issue number, then page number

PHARMACOLOGY WATCH

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

Are 5-α Reductase Inhibitors Associated with Hip Fractures?

In the issue: 5-α reductase inhibitors and hip fracture in men; the effects of drug-reimbursement policy on outcomes; new guidelines for type 2 diabetes; beta-blocker-associated bradycardia is linked to CVD events; FDA Updates.

DO 5-α REDUCTASE INHIBITORS AFFECT BONE DENsity in men? These drugs, which include finasteride (Proscar®) and dutasteride (Avodart®), have been used for more than a decade to treat benign prostatic hyperplasia (BPH). The drugs block the conversion of testosterone to dihydrotestosterone, the more powerful androgenic agent, which is responsible for secondary sex characteristics, but also adverse effects such as BPH, acne, and male pattern baldness. The 5-α reductase inhibitors shrink prostatic tissue and improve BPH symptoms over time and also can be associated with erectile dysfunction and gynecomastia. Recently researchers looked at the correlation between use of finasteride and bone health, which is highly dependent on steroid pathways. Researchers from Kaiser Permanente in Southern California performed a population-based case-control study of 7076 men age 45 and older with incident hip fractures over a 10-year period. Control patients were 7076 men without hip fracture. The rate of BPH was the same in both groups. There was no suggestion of a dose-response relationship between exposure to 5-α reductase inhibitors and hip fracture (P = 0.12). Interestingly, there was slightly higher rate of α-blocker use in the hip fracture group. The authors conclude that exposure to 5-α reductase inhibitors is not associated with increased risk of hip fracture; in fact, there was a trend toward a protective effect. The increased risk associated with exposure to α-blockers (which can cause orthostasis) needs further investigation (Jacobsen SA, et al. Association between 5-alpha reductase inhibition and risk of hip fracture. *JAMA* 2008;300:1660-1664).

Effect of drug-reimbursement policy on health care outcomes

Researchers recently looked at clopidogrel use and health outcomes for cardiac patients before and after a Canadian provincial government changed its prior-authorization policy for medications to a more liberal limited-use policy. Researchers looked at all patients 65 years or older with acute myocardial infarction who underwent PCI with stenting. The primary outcome was composite rate of death, recurrent acute myocardial infarction, PCI, and coronary artery bypass grafting at one year. After the change in benefits, the rate of clopidogrel use for 30 days after hospitalization increased from 35% to 88% and the mean time to first dispensing of clopidogrel decreased from 9 days to 0 days. The one-year composite cardiovascular outcome decreased from 15% in the prior-authorization

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) 262-5468. E-mail: paula.cousins@ahcmedia.com.

group to 11% in the limited-use group ($P = 0.02$). The authors conclude that removal of prior-authorization leads to improvement in timely access to clopidogrel after coronary stenting and improved cardiovascular outcomes (Jackevicius CA, et al. Cardiovascular outcomes after a change in prescription policy for clopidogrel. *N Engl J Med* 2008;359:1802-1810).

Updated guidelines for type 2 diabetes

The American Diabetes Association and the European Association for the Study of Diabetes have updated their treatment guidelines and algorithms for the treatment of type 2 diabetes. Published simultaneously in *Diabetes Care* and the European journal *Diabetologia*, the guidelines update the initial August 2006 guideline and the January 2008 update to reflect safety issues surrounding the thiazolidinediones (TZDs) and also introduces new classes of medications to the algorithm. Retained as step 1 therapy are lifestyle interventions and metformin. Step 2 therapy includes insulin and sulfonylureas, while TZDs have been dropped as initial therapy. Of the two TZDs, only pioglitazone (Actos™) is recommended by the guideline. Safety concerns regarding rosiglitazone (Avandia®) have resulted in the guideline group to state: "…given that other options are now recommended, the consensus group members unanimously advised against using rosiglitazone." The GLP-1 agonist exenatide (Byetta®) is elevated to tier 2 with the guideline pointing out the advantage of weight loss associated with the drug, but also noting it is given by two injections per day, has frequent GI side effects, is very expensive, and does not have an established long-term safety history. Other drugs newly mentioned in the guideline include the α-glucosidase inhibitors (starch blockers), acarbose (Precose™) and miglitol (Glyset®); the glinides, repaglinide (Prandin®) and nateglinide (Starlix®); the amylin agonist primlintide (Symlin®); and the DPP-4 inhibitor sitagliptin (Januvia®) (Nathan DM, et al. Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm of the initiation and adjustment of therapy. *Diabetes Care* 2009;32:1-11; Available at: http://care.diabetesjournals.org/misc/dv08-9025.pdf).

Beta-blockers and hypertension

Beta-blockers have come under increasing fire for treatment of hypertension. Now a new study links beta-blocker-associated bradycardia with increased risk of cardiovascular events. Researchers from Columbia University performed a meta-analysis of 9 randomized controlled trials evaluating beta-blockers for hypertension and from which heart rate data were reported. The compiled studies included more than 34,000 patients taking beta-blockers and more than 30,000 on other antihypertensive agents, as well as nearly 4000 patients receiving placebo. Lower heart rate associated with beta-blocker use was linked to a greater risk for all-cause mortality ($r = -0.51$; $P < 0.0001$) and cardiovascular mortality ($r = -0.61$; $P < 0.001$). There was also a statistically significant increase in myocardial infarction, stroke, and heart failure associated with lower heart rates. The authors conclude that in contrast to patients with myocardial infarction and heart failure, beta-blocker-associated reduction in heart rate increases the risk for cardiovascular events and death for hypertensive patients. The authors even suggest that beta-blockers may no longer be indicated for treatment of hypertension in the absence of compelling indications (Bangalore S, et al. Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension. *J Am Coll Cardiol* 2008;52:1482-1489).

FDA Updates

The FDA has approved a new selective α-blocker for the treatment of benign prostatic hyperplasia. Silodosin is an α-1 receptor blocker with high affinity for prostate, bladder, and urethra. It will be marketed in an 8 mg dose to be given once daily; however, 4 mg should be used in men with hepatic or renal impairment. Silodosin will be marketed by Watson Pharmaceuticals as Rapaflo™.

The FDA will investigate a report for the Institute of Safe Medication Practices regarding varenicline (Chantix®), Pfizer's smoking cessation drug. For the second straight quarter, varenicline accounted for more reported serious injuries than any other prescription drug with a total of 1001 new cases reported to ISMP, including 50 deaths. The FDA has previously issued a Public Health Alert about psychiatric side effects from the drug, but the new report sites numerous cases involving vehicular or other accidents, or syncope with a high potential to cause accidents. The federal government has already taken action to ban airline pilots and military missile crews from using the drug. Sales of varenicline have dropped sharply this year as a result of these reports. ■

Clinical Briefs in
Primary Care
The essential monthly primary care update
By Louis Kuritzky, MD
Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*
VOLUME 13, NUMBER 12 PAGES 23-24 DECEMBER 2008

Early intensive anti-diabetic treatment may improve β-cell function

Source: Chen HS, et al. Beneficial effects of insulin on glycemic control and β-cell function in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy. *Diabetes Care* 2008;31:1927-1932.

Approximately 50% of β-cell function has been lost at the time of initial diagnosis of type 2 diabetes. The UKPDS suggested that neither insulin, metformin, nor oral agents demonstrated any particular advantage as far as progressive subsequent decline in β-cell function is concerned. Whether intensive initial glucose control with insulin followed by routine diabetic control with either insulin or oral agents improves control and/or β-cell function was the subject of this publication by Chen et al.

Newly diagnosed type 2 diabetics with severe hyperglycemia (n = 74) were hospitalized and received intensive basal-prandial insulin therapy to maintain near-normal fasting, preprandial, and bedtime glucose; once good glycemic control had been attained and maintained for 10-14 days, subjects were discharged and randomized to continued maintenance of tight control with basal-prandial insulin or oral agents (metformin and/or sulfonylurea titrated to maintain FBS 90-130 mg/dL).

The insulin-maintenance group had significantly greater improvements in A1c at 6 months, although FBS levels were similar to the oral agent group. A comparison of β-cell function at 6 months indicated that patients receiving basal-prandial insulin treatment had better outcomes than those on oral agents.

Evolution of management techniques for type 2 diabetes continues to suggest an earlier and more prominent role for insulin therapy. These data suggest that how one gets to goal may be important, and that early introduction of insulin may have advantages over oral agents. ■

How long should 'clear sailing' certificate last after colonoscopy?

Source: Imperiale TF, et al. Five-year risk of colorectal neoplasia after negative screening colonoscopy. *N Engl J Med* 2008;359:1218-1224.

The 2008 guidelines from the American Cancer Society (ACS) have given the green light to support a variety of different colon cancer screening tools, though colonoscopy (COL) continues to have the greatest advocacy from health professionals. The currently recommended interval for re-examination after a negative COL is 10 years in average-risk individuals. Imperiale et al looked at the yield of COL performed 5 years after an initial negative screening COL in average-risk individuals (n = 1256).

Upon rescreening, no cancers were found. Advanced adenomas were found in 1.3%; the relative risk for a new advanced adenoma was 3-fold higher in men than in women.

These data are somewhat surprising when contrasted with a recent study of individuals undergoing two colonoscopies the same day at Indiana University, in which the adenoma miss rate of colonoscopy by experienced endoscopists was 24%! Nonetheless, in neither study does it appear that frank carcinoma was missed. Although this trial does not confirm that a 10-year interval, as recommended by current ACS guideline, is appropriate, it indicates that over a 5-year interval, no new cancers were discovered. ■

The Swedish Diabetes CVD Risk Score

Source: Cederholm J, et al. Risk prediction of cardiovascular disease in type 2 diabetes. *Diabetes Care* 2008;31:2038-2043.

Cardiovascular disease (CVD) risk prediction helps to identify persons at high risk, stratify treatment groups, and motivate healthful behaviors and modification of risk factors. Diabetic patients are at particularly high risk of CVD, yet currently available risk scoring systems have not performed particularly well.

The Swedish National Diabetes Register provided the patient population from which a new CVD risk predictor has been developed.

During a mean follow-up of 5.6 years (n = 11,646 adult diabetics), 1482 first CVD events occurred. Risk factors with strong association to CVD events were confirmed to be A1c, age at onset of diabetes, duration of diabetes, gender, BMI, smoking, SBP, use of antihypertensive medication, and use of lipid-lowering medication. When these risk factors were used in randomly selected subgroups from the population, accuracy of CVD risk prediction was excellent.

Because this risk prediction tool utilizes information that is generally readily clinically available, and is structured to inform us about predicted 5-year risk (rather than 10-year risk in several other popularly used risk scores), the Swedish Diabetes CVD Risk Score may find popular utility. ■

Ethnic disparity in colon polyps detected during routine screening

Source: Lieberman DA, et al. Prevalence of colon polyps detected by colonoscopy screening in asymptomatic black and white patients. *JAMA* 2008;300:1417-1422.

Both the incidence and rate of mortality of colon cancer (CCa) is higher in black men and women than whites; CCa also occurs at a younger age in blacks than in whites. Health care access issues, lesser adherence to screening recommendations, or less frequent screening recommendations by health care providers to some minority groups might explain some—but not all—of this disparity. Sociopolitcal and economic issues aside, there may simply be a greater incidence of CCa and precancer (i.e., polyps) in black men and women.

Lieberman et al evaluated data from sites (n = 67) routinely performing screening colonoscopy in asymptomatic individuals. During the 2004-2005 interval, 80,061 white and 5464 black persons underwent screening colonoscopy. The primary endpoint of the data analysis was the prevalence of large polyps (> 9.0 mm).

Overall, black women were 62% more likely than white women to have a large polyp discovered on screening colonoscopy; black men were 16% more likely to have a large polyp found. This information should encourage clinicians to be particularly vigilant that black men and women participate in timely screening colonoscopy. ■

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

Associate Publisher: Coles McKagen. **Editor:** Stephen Brunton, MD. **Senior Managing Editor:** Paula Cousins. This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

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

AHC Media LLC

Cannabis withdrawal: Under-recognized

Source: Hasin DS, et al. Cannabis withdrawal in the United States: Results from NESARC. *Am J Psychiatry* 2008;69:1354-1363.

Opinions on the consequences of marijuana use are wide-ranging: Some experts express grave concern that it may induce COPD, increase risk of lung cancer, promote the emergence of schizophrenia, and lead to "heavy drug" use; others essentially dismiss these (potential) adversities as inadequately established to permit accusations that marijuana has any commonplace serious adverse effects. Like alcohol, where there is an established "dose-response curve," indicating that alcohol in moderation is associated with beneficial health outcomes, as opposed to excessive alcohol, which leads to numerous adverse events, there may be a particular degree of marijuana use that leads to toxicity.

There is no specific DSM-IV diagnostic code for marijuana withdrawal, perhaps reflecting the commonplace observation at the time of its publication that few reports had documented such a specific syndrome. The National Epidemiologic Survey on Alcohol and Related Conditions may change that.

During 2001-2002, live interviews were conducted with frequent cannabis users, defined as at least 3x/wk utilization (n = 2613). To make sure that discontinuation syndromes upon cessation of marijuana were not confounded by discontinuation of other substances sometimes concomitantly used (e.g, alcohol), there was a separate subgroup of "cannabis-only" users (n = 1119).

Frequent marijuana users commonly reported withdrawal symptoms in two primary patterns: a weakness-hypersomnia-psychomotor retardation constellation and an anxiety-restlessness-depression-insomnia cluster.

The incidence of withdrawal was essentially identical among cannabis-only users to that of multi-substance users. Finally, the noted withdrawal symptoms were reported to produce a significant degree of impairment. When presented with such symptoms, clinicians may need to consider marijuana withdrawal. ■

Effect of PUFAs on chronic heart failure

Source: GISSI-HF Investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure. *Lancet* 2008;372:1223-1230.

The pharmacologic treatment of chronic heart failure (CHF) is already complex, often requiring an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, aldosterone antagonist, nitrates, hydralazine, and diuretics. Despite risk reduction with each of these tools, residual risk remains substantial. Polyunsaturated fatty acids (PUFAs) may be another tool to reduce residual risk in CHF.

Some secondary prevention trials of myocardial infarction have indicated risk reduction with PUFAs use, primarily due to prevention of sudden death (attributed to antiarrhythmic properties of PUFAs). Whether similar benefits might be seen in patients with CHF was the subject of this clinical trial.

CHF patients (n = 6975) were enrolled in a randomized placebo-controlled trial of 1 g/d PUFAs (administered as one daily capsule containing eicosapentanoic acid and docosahexanoic acid). At 3.9 years (mean), there was a statistically significant 9% relative risk reduction of all-cause mortality in those who received PUFAs. The tolerability profile of PUFAs was similar to placebo. PUFAs therapy may provide meaningful risk reduction in patients with CHF. ■