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When Is it Best to Evaluate the Results of a CSF Tap Test?

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: *The tap test has variable results as a tool to assess patients with a presumed diagnosis of normal pressure hydrocephalus.*

Source: Virhammar J, et al. The CSF tap test in normal pressure hydrocephalus: Evaluation, reliability and the influence of pain. *Eur J Neurol* 2011; doi:10.1111/j.1468-1331.2011.03486x.

SOME ADULTS WITH THE CLINICAL TRIAD OF GAIT DISTURBANCE, DEMENTIA, AND urinary incontinence associated with normal pressure communicating hydrocephalus will improve after a cerebrospinal fluid (CSF) shunting procedure.[1,2] The diagnosis of normal pressure hydrocephalus (NPH) is based on the clinical examination, brain imaging, and supplementary tests of CSF circulation. One commonly used prognostic test to select patients for shunt surgery is the CSF tap test (TT): Up to 50 mL of CSF are removed by lumbar puncture, and assessments of gait, cognitive function, and urinary symptoms are performed before and after CSF withdrawal. The TT procedure and the assessments of function after the procedure vary among centers, as does the reported sensitivity of the test, which ranges from poor to only moderate.[3]

These authors aimed to identify the optimal time for gait evaluation after TT, to assess the variability between two repeated measurements and the inter-rater agreement of the gait tests chosen, and to clarify whether post-lumbar puncture pain (backache and/or headache) affects gait performance.

Forty patients under evaluation for NPH at Uppsala University Hospital in Sweden underwent TT. Standardized gait analyses were performed before and at 2, 4, 6, 8, and 24 hours after TT. Each evaluation was reported twice by two independent investigators. Twenty-seven patients (15 men and 12 women; 69%), showed improvements in gait, speed, and number

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of steps after TT that were significant. Only nine patients were constantly improved at every time of assessment after TT. At 2 hours, only 15 patients were improved; at 4 hours the number was 18; at 6 hours 23; at 8 hours 26; and at 24 hours 27. Therefore, evaluations at more than one assessment time for the individual patient increased the chance of noticing improvement. The variability between two measurements was low and the inter-rater agreement was good. Pain was notable in 50% of the patients and correlated negatively with improvement in gait speed at 2 and 8 hours after TT.

■ COMMENTARY

The authors did not determine the sensitivity of their assessments after TT in predicting which NPH patients would benefit from a CSF shunting procedure, and did not report the results of surgery in this series. The authors, however, have provided useful information to clinicians who use the TT to select patients for surgical shunting: The results of TT can be evaluated within the first 24 hours, but positive results may not be evident until the 8–24 hours period. In the first 8 hours after LP, back pain and orthostatic headache may limit the accuracy of the assessments of gait.

At present, most clinicians prefer to identify patients as either probable or improbable shunt responders on the basis of clinical history and neuroimaging techniques. A short history, a known cause of hydrocephalus, and the predominance of gait disorder rather than dementia, as well as the absence of both substantial cortical atrophy with extensive white matter involvement in a patient, predict a greater than 50% chance of responding to shunt surgery regardless of the TT results. ■

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2. Adams RD, et al. Symptomatic occult hydrocephalus with "normal" cerebrospinal-fluid pressure. A treatable syndrome. *N Engl J Med* 1965;273:117-126.
3. Relkin N, et al. Diagnosing idiopathic normal-pressure hydrocephalus. *Neurosurgery* 2005;57:S4-16.

Teriflunomide: A New Oral Agent for the Treatment of Multiple Sclerosis

ABSTRACT & COMMENTARY

By Susan Gauthier, DO, MS

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *Teriflunomide, an orally administered inhibitor of dihydro-orotate dehydrogenase, was found to be superior to placebo in reducing relapses in a 2-year, Phase 3 clinical trial in patients with multiple sclerosis.*

Source: O'Connor P, et al. Randomized trial of oral teraflunomide for relapsing multiple sclerosis. *N Engl J Med* 2011;365:1293-1303.

An active search is ongoing for the perfect "pill" to treat multiple sclerosis (MS). Patients with relapsing forms of MS typically are treated with one of four first-line injectable treatments. The major limitations related to these agents include partial efficacy (~30% reduction in relapse rate), limited data on long-term disability, and multiple side effects related to injection. Clinicians caring for patients with MS spend much time counseling patients through challenges such as injection anxiety, injection site pain/irritation, and injection fatigue. Fingolimod (Gilenya®), an oral agent recently approved by the FDA for treating MS, has limited use as a first-line agent due to a complicated safety profile. Teriflunomid is the first of a series of new oral agents in the pipeline for MS. All of these newer agents have the potential to replace the current injection therapy.

Teriflunomide is an active metabolite of leflunomide, which is used to treat patients with rheumatoid arthritis;

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

however, teriflunomide has a distinct mechanism of reversibly inhibiting dihydro-orotate dehydrogenase. As a result, there is a reduction in pyrimidine synthesis and a subsequent reduction in T- and B-cell activation and proliferation. In the study by O'Connor et al, patients with active relapsing-remitting MS were randomized (1:1:1) to receive either placebo, teriflunomide 7.0 mg, or teriflunomide 14.0 mg, and were followed for 108 weeks. Progressive patients with intervening relapses also were enrolled; however, these patients made up a small minority. The primary outcome for the study was a reduction in relapse rate, and secondary objectives included a delay in sustained disability progression as well as a reduction in number of standard MRI measures. The dropout rate for this study was high (between 25%-29%), yet similar across all treatment groups. There was a 31.2% ($P < 0.001$) and 31.5% ($P < 0.001$) relative risk reduction in annualized relapse rate in patients treated with 7.0 mg and 14.0 mg of teriflunomide, respectively, compared to placebo. A significant benefit on sustained disability was found only within the high-dose group (30% reduction at 2 years, $P = 0.03$). There was a 39.4% ($P = 0.03$) and 67.4% ($P < 0.001$) relative risk reduction in new T2 lesions and a 57% ($P < 0.001$) and 80% ($P < 0.001$) relative reduction in new gadolinium-enhanced lesions per scan in the low- and high-treatment groups, respectively, compared to placebo. There was no significant benefit of teriflunomide on the rate of brain atrophy. The most common adverse events related to teriflunomide (with a dose-response effect) were diarrhea, nausea, hair thinning or decreased hair density, and elevated alanine aminotransferase. The rate of mildly elevated alanine aminotransferase was very common (≥ 1 times occurred in 54.0% and 57.3%, respectively), but the incidence of ≥ 3 times was similar across placebo and treatment groups (6.3%, 6.7%, and 6.7%, respectively). There was only a slight reduction in lymphocyte counts in teriflunomide-treated patients that stabilized after 3 months. Importantly, the rate of serious infections was similar among all groups (2.2%, 1.6%, and 2.5%, respectively).

■ COMMENTARY

This was a well-designed study that demonstrated a beneficial effect of teriflunomide in relapsing forms of MS. Surprisingly, infections were not found to be higher in the active treatment cohort and the drug appears to be fairly well tolerated. The results from this study are similar to those of the pivotal trials for the current injectable therapies; therefore, it doesn't appear that an efficacy advantage has been gained with teriflunomide. Is there a side effect advantage of teriflunomide over the injections? Considering the gastrointestinal side effects and hair thinning associated with teriflunomide, we will need "real world" patient experience to answer this question. Thus, it has yet to be determined if teriflunomide will be the "pill to end injections" for patients with MS or if other agents in the pipeline are better candidates. ■

Rituximab May Be Effective for Refractory Myasthenia Gravis

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: *In a restrospective review, rituximab appeared beneficial for patients with medication-resistant myasthenia gravis.*

Source: Nowak RJ, et al. Response of patients with refractory myasthenia gravis to rituximab: A retrospective study. *Ther Adv Neurol Disord* 2011:4:259-266.

What can you offer the refractory myasthenia gravis (MG) patient when plasma exchange, intravenous immunoglobulin, corticosteroids, mycophenolate mofetil, azathioprine, and cyclosporine fail to produce remission? In a retrospective review of 14 refractory, generalized, MG patients seen at the Yale Neuromuscular Clinic between 2003-2009 — six patients who were antibody-positive for acetylcholine receptor and eight patients positive for muscle specific tyrosine kinase — rituximab, a monoclonal B-cell-directed antibody, appears to have been efficacious. Refractory MG was defined either as symptomatic despite medication, as an inability to lower immunomodulatory medication without relapse, or by the presence of significant side effects due to immunomodulatory medication. Patients were examined pre- and post-rituximab administration, and response was determined by comparing symptoms and examination findings before and after treatment. Standard dosing of rituximab was administered at 375 mg/m^2 weekly for 4 weeks, with 6-month intervals between treatment courses. Statistical evaluation included t-test analysis, with $P < 0.05$ considered significant.

Among 13 patients who were prednisone-dependant, rituximab infusion allowed eight to taper off steroid medication completely, five by the second cycle, and an additional three by the third cycle. Plasma exchange treatments were also significantly reduced in frequency, with

Stroke Alert: A Review of Current Clinical Stroke Literature

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

Extracranial-Intracranial Bypass Surgery is No Better Than Medical Therapy for Stroke Prevention

Source: Powers WJ, et al, for the COSS Investigators. Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia. The Carotid Occlusion Surgery Study randomized trial. *JAMA* 2011;306:1983-1992.

Forty-nine clinical centers and 18 positron emission tomography (PET) centers in the United States and Canada participated in a randomized, blinded-adjudication clinical treatment trial of 195 patients with symptomatic atherosclerotic internal carotid artery occlusion (AICAO) who also had hemodynamic cerebral ischemia identified by ipsilateral increased oxygen extraction fraction measured by PET. Anastomosis of a superficial temporal artery branch to a middle cerebral artery cortical branch was performed in the surgical group and all patients were treated with antithrombotic therapy and risk factor interventions as appropriate. Primary outcome measures were (1) all stroke and death from surgery (or randomization) through 30 days, and (2) ipsilateral ischemic stroke within 2 years of randomization.

The trial was terminated early for futility. Two-year rates for stroke were 21.0% (95% confidence interval [CI], 12.8% to 29.2%) for the surgical group and 22.7% (95% CI, 13.9% to 31.6%) for the medical group (P = 0.78). Thirty-day stroke rate for the surgical group was 14.4% and 2.2% in the medical group. In this trial, bypass surgery did not reduce the risk of recurrent stroke at 2 years. These results are similar to the trial reported in 1985 (*N Engl J Med* 1985;313:1191). ■

Overweight May Be Associated with a Reduced Risk of Aneurysmal Subarachnoid Hemorrhage

Source: Sandvei MS, et al. Risk factors for aneurysmal subarachnoid hemorrhage — BMI and serum lipids: 11-year follow-up of the HUNT and the Tromso Study in Norway. *Acta Neurol Scand* DOI: 10.1111/j.1600-0404.2011.01578.x.

Lifestyle factors, including smoking, hypertension, and excessive alcohol intake, have been associated with increased risk for aneurysmal subarachnoid hemorrhage (aSAH). In this study, investigators analyzed the impact of body mass index (BMI) and serum lipids on the risk of aSAH in a prospective cohort of 102,408 participants in two large population health studies from Norway. Measurements included body weight and height, serum lipids, and self-administered questionnaires. Participants who subsequently experienced aSAH were identified and hazard ratios were calculated.

During 11 years of follow-up, aSAH was identified in 122 cases, and overweight (BMI 25-29.9 kg/m^2) was negatively associated with the risk of aSAH (hazard ratio 0.7: 95% CI, 0.4 to 1.0). There was no association with total serum cholesterol, HDL, or triglycerides with the risk of aSAH, but in persons < 50 years of age, HDL was inversely associated with risk of aSAH. This study also confirmed previously noted risk factors, including female gender, hypertension, smoking, and excessive alcohol consumption. ■

nine and 11 patients no longer requiring them at 6 and 12 months, respectively. After one cycle of rituximab, mycophenolate mofetil could be discontinued in the single patient who was so treated, and azathioprine could similarly be discontinued in two of four such patients, after one and two cycles in each patient, respectively. Antibody titers dropped by a mean of 52.1% after two cycles of rituximab, and clinical improvement was evident in tandem with decreased medication requirements and falling antibody titers. Rituximab was safe, with only six adverse events among a total of 132 infusions, comprising chills and rigors (n = 3, all in the same patient during sequential infusions), and one each, in individual patients, of flushing and pruritis, flushing and dyspnea, and a hot sensation throughout the body in the absence of flushing. Rituximab appears to be a safe and efficacious therapeutic option in refractory myasthenia gravis.

■ COMMENTARY

Tacrolimus (Prograf) often is mentioned as yet another steroid-sparing agent that may be useful in MG. However, among 80 stable myasthenic patients, on the equivalent of 10-20 mg/day of prednisolone, and randomized in a double-blind, placebo-controlled, parallel group, 28-week study, no significant difference was observed between the placebo and active treatment group (tacrolimus 3 mg po

Intra-Arterial Therapy for Acute Ischemic Stroke Does Not Increase the Risk of Symptomatic Intracranial Hemorrhage

Source: De Marchis GM, et al. Intracranial hemorrhage, outcome, and mortality after intra-arterial therapy for acute ischemic stroke in patients under oral anticoagulants. *Stroke* 2011;42:3061-3066.

SYMPTOMATIC INTRACRANIAL HEMORRHAGE (SICH) IS THE most feared complication of thrombolysis for acute ischemic stroke (AIS), and has been documented to occur in 5% to 7% of patients who are treated in intravenous tPA. Current guidelines recommend the use of IV tPA in patients who have an INR < 1.7, and many patients being treated with oral anticoagulants (OAC) are referred for intra-arterial therapies (IAT), which include locally applied thrombolysis or mechanical clot extraction. A recent study (*Arch Neurol* 2010;67:559) noted that the risk of sICH was increased by 10-fold in all patients being treated with OAC who then received IV tPA, even if their INR was less than 1.7. This study examined the risk of hemorrhagic complications after intra-arterial therapies for AIS in patients who were receiving OAC.

In this study, 714 consecutive patients were treated with IAT at a single center in Bern, Switzerland, from 1992 to 2010. Twenty-eight patients (3.9%) were taking OAC at the time of AIS symptom onset. Median INR in the OAC group was 1.79 and 1.01 in the group without OAC. Patients treated with OAC on admission were more often treated with mechanical-only clot extraction (46.4% vs 12.8%). Comparing patients with or without previous use of OAC, there was no statistically significant difference in the rate of sICH (7.1% vs 6.0%), unfavorable outcome as measured by the modified Rankin Scale (67.9% vs 50.9%), or mortality (17.9% vs 21.6%). ■

Intraventricular tPA Can Be Safely Administered Via Ventricular Catheter to Patients with Intracerebral and Intraventricular Hemorrhage

Source: Naff N, et al. Low-dose recombinant tissue-type plasminogen activator enhances clot resolution in brain hemorrhage. The intraventricular hemorrhage thrombolysis trial. *Stroke* 2011;42:3009-3016.

INTRACEREBRAL HEMORRHAGE (ICH) CARRIES A HIGH MORtality (50%) and intraventricular extension (IVH) makes the prognosis worse. The investigators used a clot lysis protocol by administering tPA via ventricular catheter to enhance resolution of the hematoma. Forty-eight patients at 14 centers were randomized to treatment with 3 mg of tPA given every 12 hours, and compared to a group with ventricular drainage alone. Clinical features were evenly distributed, including Glasgow Coma Scale, ICH volume, IVH volume, and blood pressure. There were no differences between the groups in intracranial pressure or cerebral perfusion pressure.

In both groups, the frequency of death (18% rtPA; 23% placebo) and ventriculitis (8% vs 9%) was lower than expected and symptomatic bleeding was higher in the tPA group (23% vs 5%). Median duration of dosing was 7.5 days for tPA and 12 days for placebo, indicating a beneficial effect of tPA on clot resolution. This study was not designed to assess functional outcomes and a larger Phase 3 trial will be needed to fully evaluate the potential benefit of this therapy. ■

daily) with respect to the primary endpoint of mean daily prednisolone dose given in the last 12 weeks of the study. Effective steroid sparing with tacrolimus was suggested by secondary analysis, comprising mean daily prednisolone dose every 4 weeks, mean prednisolone dose in mg/kg in the last 4 weeks, and total prednisolone dose given during the trial.[1] Further study is necessary before tacrolimus can be recommended as a steroid-sparing agent in MG. ■

Reference

1. Yoshikawa H, et al. Randomised, double-blind, placebo-controlled study of tacrolimus in myasthenia gravis. *J Neurol Neurosurg Psychiatry* 2011;82:970-977. Erratum in *J Neurol Neurosurg Psychiatry* 2011;82:1180.

Surgical Treatment of Brain Metastases

ABSTRACT & COMMENTARY

By William Cobb, MD, and Theodore H. Schwartz, MD, PhD

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Dr. Cobb and Dr. Schwartz report no financial relationships relevant to this field of study.

Synopsis: *Surgical removal of brain metastases remains an important part of palliative therapy for metastatic cancer.*

Source: Rogne SG, et al. Craniotomy for brain metastases: A consecutive series of 316 patients. *Acta Neurol Scand* DOI:10.1111/j.1600-0404.2011.01590.x.

BRAIN METASTASES ARE THE MOST COMMON TYPE OF BRAIN tumor; more than 100,000 people are diagnosed with metastatic brain tumors in the United States each year. Metastatic lesions are diagnosed in as many as one-third of cancer patients, which portends a poor prognosis in general. Overall median survival from the time of diagnosis is approximately 7 months, making metastatic brain tumors a significant health concern. Treatment usually consists of surgical resection followed by whole brain radiation therapy (WBRT), although stereotactic radiosurgery has recently become more frequent for initial upfront treatment and WBRT can sometimes be avoided in a subpopulation of patients.

In the article by Rogne et al, the authors investigated the role of craniotomy as the initial treatment for brain metastases, determined the overall survival and surgical mortality, and identified prognostic factors in this patient population. In their series, 316 patients from 2003 to 2009 underwent craniotomy for treatment of cerebral metastases at the Oslo University Hospital and its associates in Norway. Data on gender, age, number, location, histology, extent of disease, performance scores, and postoperative radiation treatment were collected for each patient and evaluated by uni- and multivariate analysis.

The authors found the annual incidence of craniotomy for treatment of brain metastases in Norway to be 2.6 craniotomies/100,000 inhabitants per year. Patients with primary melanoma and lung cancer had the highest likelihood of undergoing craniotomy while non-melanoma skin cancer, prostate cancer, and upper gastrointestinal cancer had the lowest. The mortality rate within 30 days of the procedure was 3.8%, half of which was directly related to surgery. Median overall survival of all patients was 9.2 months. Negative prognostic indicators included Karnofsky score ≤ 7, age > 65, multiple lesions, metastases in eloquent areas, uncontrolled primary disease, and extracranial metastases. RPA classification, which is a composite of Karnofsky score, age, and extent of disease, was shown to be the most important prognostic indicator, in that median survival for RPA Class I, II, and III were 16.2, 8.9, and 5.6 months, respectively. In addition, postoperative whole brain radiation treatment was found to improve overall survival. Those factors that had no correlation to overall survival included histology, gender, supra- vs infratentorial location, and known primary.

■ **COMMENTARY**

These authors provide population-based data that reconfirm the findings of a myriad of other studies. There is little new information here. As cancer treatment evolves, it becomes more apparent that each patient must be treated as an individual based on the specific characteristics of his or her disease and that each treatment paradigm must be tailored accordingly. Poor performance score, older age, multiple lesions or tumors in eloquent areas, extent of systemic disease, and lack of radiation therapy portend a decreased survival, which is in agreement with the existing literature. Interestingly, the authors did not find a difference when analyzing survival based on histology of the metastatic brain tumor. This is surprising given the high degree in variation in the aggressiveness of different types of cancers and the response of different cancers to whole brain radiation. This may result from the small sample size of the study where some of the histological subtypes had fewer than 20 patients. A larger sample size might show a statistically significant difference in the overall survival between different histological types of metastatic brain tumors. One factor found to have a positive effect on overall survival was postoperative radiation therapy; however, not all of the patients received the same postoperative radiation treatment. Twenty-six of the 316 patients received radiation therapy other than WBRT alone and 46 received no radiation therapy at all. There is clearly a selection bias here, and the authors provide no explanation for why some patients received radiation therapy and others did not. Hence, this conclusion is suspect. Further studies will be needed to fully elucidate the benefits of WBRT in the treatment of metastatic brain tumors and which patients can be treated with more focal therapy followed by WBRT only at relapse. Overall, the current paper reconfirms what has already been well-described in cancer patients with metastatic brain lesions. ■

Women with Migraine: Options for Decreasing Disability

ABSTRACT & COMMENTARY

By Dara Jamieson, MD

Synopsis: *Menstrually related migraine is difficult to treat and options are limited. Hormonal manipulation is controversial and unproven.*

Sources: Cady RK, et al. Sumatriptan-naproxen sodium for menstrual migraine and dysmenorrhea: Satisfaction, productivity, and func-

tional disability outcomes. *Headache* 2011;51:664-673. Allais G, et al. Perimenstrual migraines and their response to preventive therapy with topiramate. *Cephalalgia* 2011;31:152-160. Nappi RE, et al. Effects of an estrogen-free, desogestrel-containing oral contraceptive in women with migraine with aura: A prospective diary-based pilot study. *Contraception* 2011;83:223-228.

Treatment of menstrually related migraine (MRM) is especially challenging. For women with MRM, the head pain may be just one component of their monthly disability. A sumatriptan/naproxen sodium combination tablet was used to treat MRM associated with dysmenorrhea during the mild headache pain phase. In two multicenter, randomized, double-blind, placebo-controlled trials, women with menstrual migraine and dysmenorrhea treated a single menstrual migraine attack with a single fixed-dose tablet of sumatriptan 85 mg and naproxen sodium 500 mg or placebo. Participants randomized to sumatriptan-naproxen sodium were significantly more satisfied with the treatment than those randomized to placebo at 24 hours post-dose, as demonstrated by higher satisfaction subscale scores for efficacy, functionality, and ease of use. Use of sumatriptan-naproxen sodium for treatment of MRM and dysmenorrhea also was associated with lower reported "lost-time equivalents" in work and leisure time, and lower rates of functional disability compared with placebo.

Preventive treatment with topiramate is effective for overall reduction of migraine frequency, but data from premenopausal women as a subgroup of the Prolonged Migraine Prevention with Topiramate (PROMPT) study were analyzed to determine whether topiramate can specifically prevent MRM. After a 1- to 2-month prospective baseline period, 198 women with MRM received open-label topiramate (50-200 mg/day) for 6 months. During topiramate treatment, mean monthly migraine frequency was reduced from 7.03 at baseline to 4.36 (mean change: -2.66; $P < 0.001$, endpoint analysis). Mean percentage reductions were similar for migraines during and outside the perimenstrual period (-45.9% and -46.1%, respectively). In women with migraine with aura (MWA), reductions in migraine days with or without aura were similar to those in women without aura. Reductions in days of headache also were not affected by the use of combined oral contraceptives (COCs). Topiramate treatment did not affect migraine duration and there was only minor reduction in severity of the headache. Topiramate reduces the frequency, but not severity or duration, of perimenstrual migraines in women with MRM, including migraines with and without aura and without regard to COC use.

MWA is associated with an increased risk of ischemic stroke and to a lesser extent coronary artery disease, and the use of COCs is often avoided, especially in women with MWA and other vascular risk factors of hypertension and smoking. Women who have migraine without aura may develop auras with the use of COCs. The progestogen-only contraceptive pill (POP) appears to be a safe alternative to COCs in these women. In a prospective diary-based pilot study, 30 women with MWA (half were COC naive) were followed for 9 months. After a 3-month run-in period, each subject received an estrogen-free desogestrel (DSG) (75 mcg/day)-containing OC. Follow-up evaluations were planned at the end of the third and sixth month of treatment. The number (mean $\pm$ SD) of migraine attacks was significantly reduced both in previous COCs users (from 3.9 ± 1.0 to 2.9 ± 0.8; $P < 0.001$) and nonusers (from 3.2 ± 0.9 to 2.6 ± 1.3; $P < 0.02$) following 6 months of POP use, in comparison with the run-in period. Duration of headache pain did not differ significantly between both groups throughout the study. A beneficial POP effect on the duration of visual aura (from 16.3 ± 9.5 to 11.4 ± 5.6 min) and on the total duration of neurological symptoms (from 33.6 ± 23.3 to 18.6 ± 18.0 min) was only significant in previous COC users at the end of the study period. There was a trend toward decreased analgesic use and vomiting associated with the POP. The POP was well-tolerated by women in both groups and breakthrough bleeding was infrequent.

COMMENTARY

The majority of the approximately 30 million American migraine sufferers are women and about 20% of all women are at least periodically disabled by migraines. The most problematic migraines for women are menstrual migraines, which tend to be more severe than episodic migraine, and MWA, which are physically debilitating and concerning because of their association with increased vascular risk. Strategies to treat migraine in women combine lifestyle modifications and medications, both acute and preventive, with hormonal manipulation to decrease the impact of falling estrogen or estrogen withdrawal in triggering headaches. These papers offer options to treat women with migraine headaches. Both placebo-controlled studies of the efficacy of sumatriptan/naproxen sodium combination tablet and topiramate in patients with MRM refine our knowledge of these medications. Although positive results compared to no treatment are not unexpected, MRM headaches last longer, are more disabling, and are less responsive to treatment than other migraines. More information is needed from head-to-head comparison of different acute and preventive treatments to decrease the time spent trying various treatment strategies for women with migraine.

Contraception in women with active MWA is problematic, since the vascular risk of pregnancy exceeds the vascular risk of the combination of MWA and COCs, and since stroke in women who have MWA is generally associated with a good functional outcome. Menstrual suppression with COCs is an option to decrease MRM for some women, but this option is generally limited to women who do not have active MWA. The POP seems to offer

decreased vascular risk with slightly decreased pregnancy protection, although its use may not be satisfactory to some women as compared to the benefits of COCs. ■

CME Objectives

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

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

CME Instructions

To earn credit for this activity, follow these instructions:

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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. Which of the following statements regarding TT is *not* true?

a. some patients did not show improvement for up to 24 hours.
b. back pain and orthostatic headache interfered with some assessments.
c. 69% of the patients responded to CSF shunting.
d. more than one assessment should be performed if gait does not initially improve.
e. some patients improved as early as 2 hours after lumbar puncture.

2. Which one is *not* an adverse event associated with teriflunomide?

a. Lymphopenia
b. Hair thinning
c. Nausea
d. Diarrhea
e. Elevation of alanine aminotransferase

3. Which of the following medications may be useful for the treatment of myasthenia gravis?

a. Mycophenolate mofetil
b. Azathioprine
c. Cyclosporine
d. Rituximab
e. All of the above

4. Duration of survival after surgical removal of a brain metastasis depends on the size of the brain lesion.

a. True
b. False

5. Which of the following statements is *true*?

a. Topiramate reduces both the severity and duration of menstrual migraine pain.
b. All oral contraceptives are contraindicated in women with migraine with aura.
c. Progestin plays a major role in the etiology of menstrually related migraine.
d. The progestogen-only contraceptive pill decreases both frequency and duration of migraines.
e. The combination of sumatriptan–naproxen sodium improves functioning in women with menstrual migraine and dysmenorrhea.

6. PET analysis of cerebral hemodynamics can select patients who will benefit from extracranial-intracranial bypass surgery.

a. True
b. False

7. Smoking, hypertension, excessive alcohol, and obesity are all risk factors for aneurysmal subarachnoid hemorrhage.

a. True
b. False

8. Intra-arterial therapy for acute ischemic stroke does not result in a higher rate of brain hemorrhage, even in patients who are taking oral anticoagulants.

a. True
b. False

9. External ventricular drainage appears to be beneficial in the treatment of intracerebral hemorrhage.

a. True
b. False

In Future Issues: **Neurocritical Care**

PHARMACOLOGY WATCH

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

HPV Vaccine Now Recommended for Males

In this issue: New recommendations for HPV vaccine; guidelines for treatment of essential tremor; updates on smoking cessation drugs; and FDA actions.

HPV vaccine and anal cancer risk

The human papillomavirus (HPV) vaccine is routinely administered to adolescent girls; now the CDC's Advisory Committee on Immunization Practices is recommending the vaccine for 11- and 12-year-old boys as well. The vaccine has been approved for use in both adolescent girls and boys to protect them against HPV but has been somewhat underutilized in girls and rarely used in boys. HPV causes genital warts and cervical cancer in women and the vaccine effectively reduces the rate of both. The vaccine is generally recommended for 11 and 12 year olds when they get other routine vaccines, and before they become sexually active. Although the vaccine is approved for boys, the CDC had not made a recommendation on routine use until now. After evaluating data on efficacy in males, the committee felt that the vaccine could protect boys against genital warts, as well as throat and anal cancer caused by HPV, and could help prevent spread of the virus to girls.

In related news, a new study shows the HPV vaccine is effective in preventing anal intraepithelial neoplasia in men who have sex with men. In a double-blind study of 602 men (ages 16-26) who have sex with men, half were randomized to the quadravalent HPV vaccine and half to placebo. The vaccine reduced the risk of anal intraepithelial neoplasia caused by the four subgroups of HPV covered by the vaccine (HPV-6, 11, 16, and 18) by half in the intention-to-treat population and by 77% in the per-protocol population. Anal intraepithelial neoplasia caused by HPV of any type was reduced by 25.7% and 54.9%, respectively. Rates of anal intraepithelial neoplasia per 100 person years were 17.5 in the placebo group and 13 in the vaccine group in the intention-to-treat, and 8.9% placebo vs 4.0% vaccine in the per-protocol population. The rate of grade 2 or 3 anal intraepithelial neoplasia related to HPV subtypes covered by the vaccine was reduced by 54.2% (intention-to-treat) and 74.9% (per-protocol). The vaccine was well tolerated. The authors conclude that the HPV vaccine reduced the rate of anal intraepithelial neoplasia in men who have sex with men and may help reduce the risk of anal cancer (*N Engl J Med* 2011;365:1576-1585). ■

Treatment of essential tremor

The American Academy of Neurology has published its updated guideline for the treatment of essential tremor. Propranolol and primidone remain first options with a Level A recommendation (established as effective). Alprazolam, atenolol, gabapentin as monotherapy, sotalol, and topiramate are graded as Level B (probably effective), while nadolol, nimodipine, clonazepam, botulinum toxin a, deep brain stimulation, and thalamotomy remain as level C (possibly effective). There is not enough evidence to make a recommendation for gamma knife therapy. The new guideline also states that there is insufficient evidence to support or refute the use of pregabalin, zonisamide, or clozipine. Levetiracetam and 3,4 diaminopyridine are ineffective and flunari-

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zine is probably ineffective. The guideline was published online in *Neurology* October 19, 2011 (doi: 10.1212/WNL.0b013e318236f0fd). ■

Chantix and neuropsychiatric side effects

There is good news for the smoking cessation drug varenicline (Chantix). Following concern about neuropsychiatric side effects, the FDA sponsored two epidemiologic studies that evaluated the risk of neuropsychiatric hospitalizations associated with the drug. Neither study found a difference in risk of neuropsychiatric hospitalization between varenicline and nicotine replacement therapy, although hospitalization was the only endpoint evaluated and they did not rule out an increased risk of other neuropsychiatric events. While reassuring, the FDA is recommending that health care professionals and patients continue to follow the recommendations previously established and monitor for neuropsychiatric symptoms when prescribing or using varenicline. The manufacturer is conducting a large safety study of the drug to assess neuropsychiatric adverse effects but the results will not be available until 2017 (www.fda.gov/Drugs/DrugSafety/). In related news, the inexpensive partial nicotine agonist cytisine is an effective adjunct to smoking cessation, according to a new study in the *New England Journal of Medicine*. Cytisine is extracted from the seeds of *Cysisus laborinum L.* (Golden Rain acacia) and has been available worldwide for years, particularly in Eastern Europe, where it can be purchased for $6-$15 per course. Researchers randomized 740 smokers to cytisine or matching placebo for 25 days along with counseling. The rate of sustained 12 months abstinence was 8.4% in the cytisine group compared with 2.4% in the placebo group ($P = 0.01$). GI side effects were slightly more prevalent in the treatment group. The authors conclude that cytisine was more effective than placebo for smoking cessation and may be "an affordable treatment to advance smoking cessation globally" (*N Engl J Med* 2011;365:1193-1200). ■

FDA Actions

The FDA is continuing to review the association of oral contraceptives and thrombotic risk, particularly oral contraceptives containing drospirenone. On October 27, the FDA issued a preliminary Drug Safety Communication, with the full report due out in early December. Reviewing the records of Kaiser Permanente members in California and state Medicaid programs in Tennessee and Washington, which included 835,826 women receiving contraceptive prescriptions from 2001-2007, an increased risk of venous thromboembolism (VTE), deep venous thrombosis, and pulmonary embolism was noted with several contraceptives, with low estrogen hormonal contraceptives as a reference. Products containing drospirenone had relative risk of VTE of 1.74 (95% confidence interval [CI] 1.42-2.14). The norelgestromin/ethinyl estradiol transdermal patch was associated with relative risk of 1.55 (95% CI 1.17-2.07) and etonogestrel/estradiol vaginal ring was associated with a relative risk of 1.56 (95% CI 1.02-2.37). The risk was higher in younger users then older women (www.FDA.gov./DRUGS/DrugSafety/ucm277346.htm).

The FDA has approved the first generic olanzapine (Zyprexa) to treat schizophrenia and bipolar disorder. The generic carries the same warnings as the brand regarding increased risk of death in elderly people with psychosis or dementia. Generic olanzapine will be available from several manufacturers as tablets and orally disintegrating tabs.

The FDA has announced that drotrecogin alfa (Xigris) is being withdrawn from the market by Eli Lilly & Co. The withdrawal is based on the results of the recently completed PROWESS-SHOCK trial in which drotrecogin alfa failed to show a survival benefit in patients with severe sepsis and septic shock. The FDA is recommending that the drug should be stopped in any patients currently being treated and should not be initiated in new patients. All remaining product should be returned to the supplier.

The FDA has approved tadalafil (Cialis) for the treatment of benign prostatic hyperplasia (BPH) either alone or when it occurs along with erectile dysfunction (ED). The drug was approved in 2003 for treatment of ED. The approval was based on two trials in which men taking tadalafil 5 mg daily experienced significant improvements in BPH symptoms compared with those taking placebo. A third study in which men had both BPH and ED, tadalafil 5 mg daily improved both symptoms of BPH and ED compared to placebo. Tadalafil should not be used in patients taking nitrates or in combination with alpha blockers for the treatment of BPH.

The FDA has approved a combination of sitagliptin and simvastatin for the treatment of adults with type 2 diabetes and hypercholesterolemia. This represents the first combination drug for treating these two conditions. The fixed dose combination is available in three strengths: 100 mg sitagliptin/10 mg simvastatin, 100 mg/20 mg, and 100 mg/40 mg. The approval was based on "substantial experience with both sitagliptin and simvastatin" and is a "convenience combination," according to the FDA. Sitagliptin/simvastatin will be marketed as Juvisync by MSD International GmbH Clonmel in Tipperary, Ireland. ■

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, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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Lifetime Risk of Developing COPD: A Longitudinal Population Study

Source: Gershon AS, et al. Lifetime risk of developing chronic obstructive pulmonary disease: A longitudinal population study. *Lancet* 2011;378:991-996.

WORLDWIDE, CHRONIC OBSTRUCTIVE pulmonary disease (COPD) is the fourth most common cause of death, and is predicted to become the third most common cause in the near future, especially if smoking habits in populous nations like China — where more than half of adult men are currently smokers — continue on their same trajectory. According to Gershon et al, no prior publications have provided adequate insight into the lifetime risk of developing COPD. Hence, using health administrative data from the entire population of Ontario, Canada (n = approximately 13 million), they reported on a 14-year follow-up of persons who did *not* have COPD at baseline.

Based on the window of observation from 1996-2010, the population was divided categorically into: a) physician-diagnosed COPD, b) reached age 80 without a COPD diagnosis, or c) death. By age 80, more than one-fourth (28%) of persons free of COPD at baseline had been diagnosed with COPD by a physician. To put this into perspective, a new diagnosis of COPD was more likely than congestive heart failure, acute myocardial infarction, or even diabetes.

The authors mention that they have observed less public awareness of COPD than might be merited based on its epidemiological presence, and they encourage greater energies be invested in smoking cessation and public education about COPD. ■

The Burden of Painful Diabetic Peripheral Neuropathy

Source: Abbott CA, et al. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. *Diabetes Care* 2011;34:2220-2224.

RECENTLY PUBLISHED TELEPHONE SURVEYS of large populations of diabetics indicate a low level of recognition of the diagnostic terminology "Diabetic Neuropathy," despite commonplace problematic symptoms consistent with this disorder. Diabetic peripheral neuropathy (DPN) and diabetic peripheral neuropathic pain (DPNP) are associated with major morbidities. For instance, the leading cause of amputation in diabetics is foot ulcer subsequent to impaired sensation in the feet from diabetic neuropathy. Similarly, DPNP is often worsened by activity, which tends to compromise exercise capacity and may also interrupt sleep.

The North-West Diabetes Foot Care Study screened 15,692 adult diabetics in northwest England. The presence of neuropathy was established using scoring systems as well as specific nerve function testing (vibration, pin-prick, temperature, and reflex testing). Screenings took place during routine annual evaluations by primary care clinicians.

Overall, one-third of study subjects experienced painful neuropathy. DPNP was twice as common in persons with type 2 diabetes than type 1. Women and persons of South Asian ethnicity were disproportionately affected. Based on these findings, clinicians might anticipate an important positive yield from routinely screening for symptoms of DPNP and signs of DPN. ■

Predictive Value of Postprandial Glucose for CV Events in Type 2 Diabetes

Source: Cavalot F, et al. Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: Lessons from the San Luigi Gonzaga Diabetes Study. *Diabetes Care* 2011;34:2237-2243.

THE DECODE DATA (DIABETES EPIDEMIOLOGY Collaborative Analysis of Diagnostic Criteria in Europe) indicated that all-cause mortality, as well as cardiovascular (CV) events, were better predicted by postprandial glucose (PPG) than fasting blood glucose (FPG). Indeed, the DECODE data set indicates a linear rise in relative risk for mortality as one progresses from normoglycemia, to impaired glucose tolerance, to frank diabetes.

Although much of the literature is consistent in finding that PPG outperforms both FPG and A1C in predicting adverse CV events (and mortality), one criticism aimed at these data reminds us that PPG data were, for the most part, obtained from oral glucose tolerance testing (OGTT). Since only a small minority of patients outside clinical trials actually have OGTT performed, obtaining a PPG after actual meals might better reflect the pathophysiology occurring in long-term

management of diabetics.

Cavalot et al report on a 14-year follow-up of type 2 diabetes patients (n = 505) in whom A1C, FPG, and PPG (*not* obtained by OGTT) were measured at baseline, seeking to discern the relationship of each of these metrics with CV events and overall mortality.

For mortality as well as CV events, both A1C and PPG were strong predictors (especially post-lunch PPG). FPG was not a good predictor. It remains to be determined whether interventions specifically targeting PPG will provide meaningful benefit beyond simple traditional diabetes control. ■

Vitamin E and Prostate Cancer

Source: Klein EA, et al. Vitamin E and the risk of prostate cancer: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2011;306:1549-1556.

Observational epidemiologic data had suggested that selenium, vitamin E, or both might reduce the incidence of prostate cancer (PCa). Based on this hypothesis, the SELECT trial (Selenium and Vitamin E Cancer Prevention Trial) was performed. The basic structure was a randomized, placebo-controlled trial of vitamin E 400 IU/d (VitE), selenium 200 mcg/d (SEL), or both in 35,533 men. Seven years after enrollment, the trial was stopped because of a lack of any demonstrated benefit along with futility analysis indicating no potential of future benefit. That was in 2008.

This report extends follow-up of the same population through 2011. At this point, a statistically significant *increased* risk of prostate cancer was seen in men taking VitE (17% increase). While the numbers for SEL as well as SEL plus VitE trended toward worse outcomes, they were not statistically significant.

Why VitE might produce an increased risk for PCa is unclear: There was, for instance, no measurable effect of VitE on PSA. Although many clinicians have opted to be essentially silent in discussions of vitamin supplements with patients — since, after all, vitE was presumed to be innocuous — these data suggest consideration of intervention to discourage VitE in healthy men. Although the data were insufficient to definitively indict selenium, there is no support for endorsing it either. ■

Is There a Relationship Between Insulin Glargine and Cancer?

Source: Morden NE, et al. Further exploration of the relationship between insulin glargine and incident cancer: A retrospective cohort study of older Medicare patients. *Diabetes Care* 2011;34:1965-1971.

Recent retrospective studies in Europe have created concern because of an observed increased risk of cancer (hazard ratio = 1.55) in users of insulin glargine (GLAR) compared to nonusers. Similarly, increased risk of breast cancer in GLAR users was reported in two other analyses (hazard ratio 1.99-3.9). These reports, in addition to the limitations of their retrospective design, also had limitations such as failure to adjust for potential confounders such as BMI, GLAR dose, the impact of socioeconomic selection bias, and the relatively short periods of observation (6 years or less).

To remedy some of the limitations of early reports, the authors reviewed a Medicare database of more than 81,000 diabetics, including a subpopulation of 16,945 on GLAR and 49,455 on insulins other than GLAR. After adjustment for recognized confounders, there was no association seen between GLAR and any cancer. Indeed, combination insulin regimens were associated with increased risk of breast cancer, an association not previously consistently identified.

The results of this large data set should be generally reassuring about the safety profile of GLAR in reference to cancer of any type. The association of breast cancer with combination insulin regimens noted here should not be considered definitive because various reports have come to conflicting conclusions. ■

Saw Palmetto and BPH: *Not*

Source: Barry MJ, et al. Effect of increasing doses of saw palmetto extract on lower urinary tract symptoms: A randomized trial. *JAMA* 2011;306:1344-1351.

Although benign prostatic hyperplasia (BPH) and its consequences are rarely a mortal concern, the quality-of-life impact of LUTS (Lower Urinary Tract Symptoms) associated with BPH is often substantial. Antihypertensive alpha blockers (e.g., doxazosin, terazosin), site-selective alpha blockers (e.g., alfuzosin, tamsulosin), and alpha-reductase inhibitors (e.g., dutasteride, finasteride) have each been shown — either alone or in combination (i.e., alpha blockers + alpha reductase inhibitors) to improve LUTS. The latter have even been shown to reduce the need for surgery and the incidence of acute urinary retention in BPH study subjects.

Despite the well-demonstrated efficacy of proprietary agents, many BPH patients opt for "natural" treatments, such as saw palmetto (SWP). An early Cochrane review (2002) of SWP was generally supportive; less positivity was reflected in the 2009 Cochrane review, because more recent, rigorous trials found lesser benefit. Most trials utilized SWP 160 mg b.i.d. Is it possible that *more* SWP might gain greater therapeutic efficacy?

Barry et al performed a randomized, double-blind trial of higher-dose SWP, including doses up to 960 mg/d. Men with BPH (n = 369) were followed for 72 weeks. At the conclusion of the trial, no beneficial effects on LUTS were seen, despite the higher dose. No serious adverse effects attributable to SWP were seen. Based on these data, SWP is not beneficial for men with BPH. ■

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NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

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