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INSIDE

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Can We Predict Pharmacoresistant Epilepsy?

ABSTRACT & COMMENTARY

By Padmaja Kandula, MD

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

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

Synopsis: *In this long-term, population-based patient series, the authors explore the natural course of drug-resistant epilepsy and explore whether remission can be predicted by clinical features.*

Source: Sillanpaa M, et al. Is incident drug-resistance of childhood-onset epilepsy reversible? A long-term follow-up study. *Brain* 2012;135:2256-2262.

DRUG-RESISTANT EPILEPSY AFFECTS NEARLY A THIRD OF EPILEPSY PATIENTS AND is defined as failure of two or more maximally tolerated, adequately chosen, anti-epileptic agents. The recommended clinical practice (2003 American Academy of Neurology Practice Parameter) is to consider referral for potential epilepsy surgery in pharmacoresistant epilepsy. However, the literature is scarce regarding the natural history of incident (new-onset) drug-resistant epilepsy. In this observational, population-based study, the authors aim to answer two questions, mainly the proportion of patients with drug-resistant epilepsy that become seizure free and the clinical features that predict seizure freedom.

Children under the age of 16 who met International League Against Epilepsy criteria for epilepsy (two or more unprovoked seizures) within the catchment area of University of Turku, Finland, up until the year 1964 were study eligible. Further inclusion criteria were well-documented and adequate anti-epileptic regimen trials, drug resistance (failure of one or two appropriate drugs used singly or in combination without seizure remission at the 2-year mark), and at least 10-year follow-up from time of epilepsy onset.

One hundred two patients ultimately met study criteria. Outcome variables, including time to and duration of seizure remission, were defined

as the following: 1-year remission ever, 2-year remission ever, 2-year terminal remission, 5-year remission ever, or 5-year terminal remission. Terminal remission was the remission at the end of follow up. Remote symptomatic epilepsy was defined as major neurological impairment or history of major neurologic insult.

Of the 102 patients, 98 had focal seizures (68 symptomatic and 30 idiopathic/cryptogenic), one had generalized convulsive seizures, and three had unclassified seizures. At the conclusion of the 40.5 year median follow-up, 82% of patients entered one or more 1-year remissions, 79% one or more 2-year remissions, 69% one or more 5-year remissions, and 51% with 5-year terminal remission. On multivariate analysis, only idiopathic/cryptogenic seizure etiology proved to be a significant predictor of seizure freedom.

■ COMMENTARY

Based on the results of this long-term study, the patients with the highest likelihood to enter terminal remission were those with idiopathic (no apparent cause) or cryptogenic epilepsy and those who have been seizure-free after incident drug-resistant epilepsy for at least 2 years. Although the advantage of this study is a very long median follow-up period, the concept that symptomatic epilepsy is often medically refractory is not new information. A large observational study by Semah et al in 1998 revealed that only a quarter of patients with structural lesions eventually became seizure-free.[1] On the other hand, the study has significant limitations largely due to the historical time frame in which the patients were initially studied. The two main limitations include the absence of MRI data (based on 1960s recruitment period) as well as limited FDA-approved anti-epileptic drug regimens. Overall, the study reinforces the need to consider early surgery in pharmacoresistant epilepsy, particularly in surgically amenable syndromes. ■

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1. Semah F, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 1998;51:1256-1262.

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

Antioxidant Supplements Are Not of Proven Benefit for Alzheimer's Disease

ABSTRACT & COMMENTARY

By Michael Lin, MD, PhD

Associate Professor of Neurology and Neurosciences, Weill Cornell Medical College

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

Synopsis: *In this well-designed, randomized, placebo-controlled clinical trial of antioxidant supplements for Alzheimer's disease, there was no benefit, and some agents were associated with worse outcome.*

Source: Galasko DR, et al, for the Alzheimer's Disease Cooperative Study. Antioxidants for AD: A randomized clinical trial with CSF biomarker measures. *Arch Neurol* 2012;69:836-841.

Given the few FDA-approved treatments for Alzheimer's disease (AD) and their very modest effects, patients frequently take a wide variety of vitamins and supplements, including antioxidants. Unfortunately, although there is extensive preclinical evidence showing benefits of antioxidants in cell and animal models of disease, experience with antioxidants in human AD trials has been mixed. In this vein, a recent trial of antioxidants by the AD Cooperative Study Group (ADCS) showed no clinical benefit. In fact, in the subgroup showing reduced oxidative stress in cerebrospinal fluid (CSF), there was actually a suggestion of more rapid cognitive decline.

The ADCS Antioxidant Biomarker study was a double-blind, randomized, placebo-controlled, multicenter clinical trial conducted at 12 academic medical centers across the United States. Seventy-eight subjects with mild-to-moderate AD (mini-mental state exam [MMSE] score 16-

30) were randomized to one of three arms. The first arm tested a combination of vitamin E (800 IU/d), vitamin C (500 mg/d), and alpha-lipoic acid (900 mg/d; E/C/ALA). Vitamin E is a lipid-based antioxidant; vitamin C is a water soluble antioxidant; alpha-lipoic acid is a mitochondrial cofactor, and also induces the nuclear respiratory factor 2 transcription factor, which in turn induces many antioxidant enzymes. Doses were chosen by an expert panel after review of the literature. The second arm tested coenzyme Q10 (CoQ) at a dose of 400 mg three times/day. CoQ is a part of the mitochondrial electron transport chain and helps to protect mitochondria from free radicals generated during oxidative metabolism. The dose chosen is the same as the dose that appeared to have benefit in a Phase 2 trial in Parkinson's disease. The third arm was the placebo arm.

All groups were well matched at baseline (mean MMSE ~23). Study medication was administered for 16 weeks. The primary outcome measures were cognition (assessed by MMSE), function (assessed by the ADCS-ADL scale), and CSF biomarkers of AD pathology (Aβ42, tau, phosphotau) and oxidative damage (F2-isoprostanes). Neither treatment had any effect on CSF biomarkers of AD pathology. The E/C/ALA treatment lowered CSF markers of oxidative damage, suggesting that the treatment penetrated the central nervous system and had the expected antioxidant effect. In contrast, the CoQ treatment had no effect on oxidative markers, suggesting either that the dose was inadequate or that oxidative stress in AD is not mediated by pathways involving CoQ. Neither treatment improved function on the ADCS-ADL scale, and CoQ did not differ from placebo in effect on cognition — both placebo and CoQ groups dropped ~1.0 point on MMSE. Of concern, however, the E/C/ALA treatment appeared to exacerbate cognitive decline, with a drop in MMSE of 2.8 points over the trial (P = 0.04), despite decreasing CSF markers of oxidative stress.

■ COMMENTARY

These results do not support further investigation into these agents or their use by patients as supplements. Further, they actually suggest discouraging use of the E/C/ALA combination, since cognitive decline was exacerbated, despite documented reduction in oxidative stress. Why this should occur is mysterious, but is at least consistent with recent meta-analyses suggesting that vitamin E in doses > 800 IU/d is associated with excess mortality. More generally, it is difficult to explain the discrepancy between theoretical understanding of the role of oxidative stress in disease pathogenesis and results of human trials. The authors note that oxidative stress is not a single specific process with an obvious single target for intervention, making it challenging to design antioxidant treatments. However, ultimately the results of human trials should guide therapy. Although patients trying multiple supplements often are doing so out of desperation, they should be counseled that no supplement has been shown to have benefit in rigorous trials, and some may actually cause harm. ■

Alternate Day Steroids for Polymyositis

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: *An alternate-day steroid protocol appears to be just as efficacious as every-day steroids over the long term in a group of patients with undifferentiated polymyositis, with less serious long-term side effects.*

Source: Uchino M, et al. Long-term outcome of polymyositis treated with high, single-dose, alternate-day prednisolone therapy. *Eur Neurol* 2012;68:117-121.

Glucocorticoids remain the cornerstone of initial therapy for polymyositis, despite the absence of placebo-controlled trials demonstrating their effectiveness, and despite the fact that older studies did not demonstrate any improvement in survival. Long-term, daily glucocorticoids result in a host of side effects, and hence alternate-day dosing is preferable. Over the short term, alternate-day dosing has been shown to be as effective as daily dosing to achieve remission.[1] Is the same true for the long-term outcome of polymyositis?

Among 235 patients with inflammatory myopathy seen between 1970-2009 at the Department of Neurology, Kumamoto University, Kumamoto, Japan, 161 had biopsy-proven polymyositis, of which 149 received either alternate-day (n = 35) or daily-dose prednisolone. Of these, 115 were followed for more than 10 years or until death, encompassing 32 alternate-day and 83 daily-dose patients, who served as the subjects of this study. Patients were excluded if there was a suspicion of inclusion body myositis, including finger, wrist flexor, or quadriceps weakness on examination, or rimmed vacuoles and amyloid deposits pathologically. Paraneoplastic necrotizing myopathy and statin-induced myopathy patients similarly were excluded, as were those who did not demonstrate classical findings on needle electromyography, including positive waves and small amplitude, short duration, polyphasic motor unit potentials. Alternate-day dosing comprised 2 mg/kg

prednisolone every other day, which was decreased by 10 mg approximately every month until a dose of 10-30 mg was achieved and maintained. Daily-dose patients underwent a similar protocol beginning at 1 mg/kg daily. Both groups were given a low-salt diet, vitamin D and potassium supplements, and anti-ulcer agents. Clinical outcome measures included manual muscle testing score using the Medical Research Council method and the six grade disability score. Statistical analysis comprised Pearson's X2 and log-rank tests with a difference of $P < 0.05$ considered significant.

Alternate-day and daily-dose groups were comparable with respect to age, disability grade, and presence of malignancy or other collagen vascular disease. Response rates were comparable between the groups, but the incidence of diabetes was significantly higher in the daily-dose group. Other adverse effects, including hypertension, hyperlipidemia, infection, osteoporosis, and psychiatric symptoms, were slightly higher in the daily-dose patients, though not significantly so. Survival rates at 20 years were significantly higher in the alternate-day group. Alternate-day prednisolone appears to be as efficacious, in polymyositis, as daily prednisolone, with fewer adverse effects, and may be considered as an initial therapeutic option.

■ COMMENTARY

Corticosteroids alone are often inadequate to treat polymyositis. Other immunosuppressive agents, including azathioprine, methotrexate, mycophenolate mofetil, rituximab, cyclosporine, cyclophosphamide, and tacrolimus, are commonly used but have never been proven efficacious in controlled clinical trials. Randomized, controlled trials have shown intravenous immunoglobulin (IVIG) to be effective in refractory polymyositis, given in the standard dose of 2 gm/kg over 2-5 days.[2] Although rarely used as initial therapy, when combined with corticosteroids, IVIG has been demonstrated to improve strength and lower creatine kinase levels compared to placebo. Hence, an approach to the treatment of polymyositis might begin with high-dose prednisone, either daily or on alternate days, followed by IVIG, azathioprine, methotrexate, or mycophenolate mofetil when needed for their steroid sparing effects. In refractory patients, rituximab, cyclosporine, cyclophosphamide, or tacrolimus would be the next option. ■

References

1. Uchino M, et al. High single-dose alternate-day corticosteroid regimens in treatment of polymyositis. *J Neurol* 1985;232: 175-178.
2. Wang DX, et al. Intravenous immunoglobulin therapy in adult patients with polymyositis/dermatomyositis: A systematic literature review. *Clin Rheumatol* 2012;31:801-806.

Frontostriatal Network Under-recruitment Underlies Mild Cognitive Impairment in Parkinson's Disease

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD, DPhil

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

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

Synopsis: *Multimodal brain imaging demonstrates extensive frontostriatal dysfunction in mild cognitive impairment in early Parkinson's disease.*

Source: Ekman U, et al. Functional brain activity and presynaptic dopamine uptake in patients with Parkinson's disease and mild cognitive impairment: A cross-sectional study. *Lancet Neurol* 2012;11:679-687.

Mild cognitive impairment (MCI) is common in Parkinson's disease (PD). Unlike dementia, it may occur early in the disease course, and often affects executive function and working memory. Unfortunately, its underlying neural substrate is not well understood, hampering rational development of therapeutics. In this cross-sectional study, drug-naïve subjects with PD were recruited from the Umea project, a longitudinal, population-based cohort of incident patients. Of these, those with PD-MCI were identified based upon scores of ≥ 1.5 SD below mean value in at least two cognitive domains during neuropsychological assessment. Healthy controls without MCI were matched for age and gender. In all, 77 subjects with PD (33 PD-MCI; 44 PD alone) and 24 control subjects were recruited. Certain subjects were further excluded to increase homogeneity of the groups (three with PD-MCI with language or visuospatial deficits as one of two affected domains, 18 with PD alone who scored below criteria on just one cognitive measure, one control subject fulfilling MCI criteria). Imaging comprised functional MRI (fMRI) during a working memory task, and ^{123}I-FP-CIT SPECT scans to evaluate integrity of the nigrostriatal presynaptic dopaminergic system. Overall, cognitive measures were significantly better in the control vs PD group, as well as in the fMRI working memory task. In those with PD both with and without MCI, fMRI blood-oxygen-level-dependent (BOLD) signal demonstrated under-recruitment of frontostriatal regions bilaterally, including right dorsolateral

prefrontal cortex, bilateral primary and premotor cortex, occipital cortex, and cerebellum, when compared with control subjects ($P < 0.001$). Comparing PD-MCI with PD alone, the presence of MCI is associated with further under-recruitment of the anterior cingulate cortex bilaterally ($P < 0.001$), the right dorsal caudate ($P = 0.005$), and more weakly with the right dorsolateral prefrontal cortex. Moreover, in the PD-MCI group, right caudate dopamine transporter density measured by ^{123}I-FP-CIT SPECT was less when compared with PD alone ($P = 0.08$).

■ COMMENTARY

The concept of PD-MCI is gaining attention and this is the first study to provide information on functional brain activity based upon fMRI. Importantly, the study makes use of recent guidelines for PD-MCI diagnosis, established by a Movement Disorder Society commissioned task force in 2012.[1] Similar to previous incident cohorts examined, PD-MCI was found to be high: 43% in this study. PD-MCI is associated with an increased risk of PD dementia (PDD). In the CamPaIGN cohort (in which 17% of incident patients developed dementia within 5 years), baseline semantic fluency and copying a pentagon were significant risk predictors.[2] PD-MCI is therefore highly concerning for patient and physician alike, yet we have only limited understanding of the underlying pathophysiology. Moreover, it is likely under-recognized, and there is no established treatment. This study is therefore important in better defining the neural substrate for PD-MCI in early PD. Longitudinal follow-up will be critical in developing a data-driven assessment of prognosis for patients in the clinic. One strength of this study is the use of rigorous inclusion/exclusion criteria, involving both clinical and neuroimaging measures, and the possibility of clinical misdiagnosis (important since it might "enrich" a so-called PD-MCI group with, for example, individuals suffering a Parkinson's Plus syndrome) was addressed by 12-60 months clinical follow-up. Unfortunately, despite the investigators' best attempts to match groups, statistically significant differences between groups existed in the degree of severity of motor symptoms (worse in the PD-MCI vs PD alone group), gender (more men were studied in the total PD and PD-MCI groups), education (higher in the control than total PD group), and mood (Montgomery-Asberg Depression Rating Scale scores were higher in the total PD than control group). In conclusion, it is important to recognize cognitive difficulties, including MCI in PD at all stages, and to openly discuss patient concerns. As yet, it remains to be established whether drugs useful in PDD would be helpful in PD-MCI. Although rivastigmine is well established in providing benefit in PDD, the role of acetylcholinesterase inhibitors and other treatments such as memantine, remain to be established in PD-MCI. PD-MCI therefore remains a critical area of need, but the present study is a significant advance in further defining PD-MCI. ■

References

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More Than Just a Number: Complexity of Intracranial Pressure Correlates with Outcome After Traumatic Brain Injury

ABSTRACT & COMMENTARY

By Halinder S. Mangat, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Analysis of intracranial pressure complexity using a non-linear method of multiscale entropy shows that it correlates with outcome after traumatic brain injury.*

Source: Lu C-W, et al. Complexity of intracranial pressure correlates with outcome after traumatic brain injury. *Brain* 2012;135:2399-2408.

Due to their complexity, data analysis of physiological signals using linear models may not accurately represent such systems. Therefore, non-linear models are gaining application in understanding the complex behavior of physiological variables such as intracranial pressure (ICP).[1] Approximate entropy[2] and wavelet entropy[3] have been applied to understand ICP changes in different clinical scenarios.

In this article, the authors apply multiscale entropy to study the correlation of ICP complexity with outcome after traumatic brain injury (TBI).[4] Briefly, entropy relates to the predictability of a variable based on previously recorded values; the higher the entropy, the more unpredictable the variable.

The authors used data from 325 patients admitted to the

neurosciences critical care unit after TBI. Time series were evolved by a graining procedure, which involved averaging consecutive data values for comparison. Averaging increasing number of consecutive data points up to 20 values created multiple time series. For each time series, sample entropy analysis was calculated, i.e., the likelihood of two similar sequences of two data points that would remain similar if a third data point was included (computed as the negative logarithm of the ratio of number of three data point pattern to the number of two data point patterns). Multiscale entropy was plotted as sample entropy for each time series against its time scale and the area under the curve was the complexity index.

There was a decrease in entropy of ICP signal and ICP complexity index across all measured scales during plateau ICP waves. ICP complexity index was significantly higher in patients who had good outcome compared with those with moderate-to-severe disability. In the multivariate logistic regression model, adding the complexity index identified it as a strong predictor of mortality. In pooled data analysis, ICP complexity index showed an inverse relationship with ICP.

■ COMMENTARY

This is the first study using multiscale entropy to study the relationship of ICP and outcome. In the comparison of data between baseline low ICP and high ICP in plateau waves, the entropy decreases as does complexity index of ICP. This supports the idea that worsening ICP changes the dynamics of ICP and at high ICP there is decomplexification of the dynamics. However, one must consider that treatment of high ICP in itself is directed to change ICP dynamics, and the effect of sedation or removing CSF may also reduce complexity of ICP signal. This is also highlighted by the fact that during plateau waves autoregulation may be severely impaired and its dynamic effect lost.[5]

Whether the loss of complexity is an exhaustion of regulatory mechanisms leading up to high ICP or this is a hallmark of high ICP remains to be determined. As the authors mention, it is difficult clinically to determine physiological interpretation of these findings. Further work using non-linear models studying one variable at a time may help to understand these.

Overall, this is an eloquent study that delves into the dynamic state and complexity of ICP, once more highlighting that ICP is much more than just a number. ■

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Mesenchymal Stem Cells Therapy for Multiple System Atrophy

ABSTRACT & COMMENTARY

By Alexander Shtilbans, MD, PhD

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *Mesenchymal stem cells for the treatment of multiple system atrophy is a promising potential therapy, but requires further investigation regarding both safety and efficacy.*

Source: Lee PH, et al. A randomized trial of mesenchymal stem cells in multiple system atrophy. *Ann Neurol* 2012;72:32-40.

MULTIPLE SYSTEM ATROPHY (MSA) IS A NEURODEGENERAtive disorder potentially resulting in pyramidal, extrapyramidal, cerebellar, and autonomic dysfunction. It is associated with deposition of cytoplasmic α-synuclein protein aggregates and loss of surrounding neurons in the brainstem, cerebellum, and basal ganglia. The course of the illness is more rapid than Parkinson's disease, averaging in 7-10 years disease duration. There is no cure and most of the cases do not respond to dopaminergic therapies. A 2008 open-label study by Lee et al has shown that autologous mesenchymal stem cell (MSC) injections could delay progression of neurological symptoms in MSA-C (cerebellar type), although the lack of blinding brought some criticism.[1] In the current study, the authors conducted a randomized, double-blind, placebo-controlled trial aimed at detecting a change in severity of neurological deficits in active and placebo groups, evaluated by total unified MSA rating scale (UMSARS) over a 360-day period. The second endpoint was a change in part II (motor) of UMSARS,

cerebral glucose metabolism, gray matter density, and cognitive performance. The authors recruited 33 patients with probable MSA-C and randomized them to the active and placebo groups. Fourteen patients received intra-arterial and intravenous mesenchymal stem cell injections and 17 patients received placebo in similar fashion. Of the 14 patients in the active arm of the study, 11 completed the trial, whereas 16 patients from the placebo group completed the trial. The most common side effects associated with the infusions were acute cerebral ischemic lesions seen on DWI MRI sequences performed immediately after the intra-arterial infusions. Those lesions were seen in 29% of the MSC treated patients and in 35% of placebo patients. Clinical assessments were performed at baseline and at 30, 60, 90, 120, 150, 180, 240, 300, and 360 days after the initial injection. The patients who received stem cell therapy showed a statistically significant smaller increase in the total and part II UMSARS scores compared to the placebo group. There was no statistically significant difference in the UMSARS part I addressing quality of life. FDG PET scans showed a smaller decrease in glucose metabolism in the cerebellum of the patients in the active group of the trial. The stem cell group also had more preservation of the gray matter density during the follow-up period than the placebo group. Neuropsychological evaluation showed that the stem cell group had no significant deterioration of cognitive performance compared to worsening cognitive functions in the placebo group. The post-hoc analysis showed the most significant difference in the total UMSARS score between the MSC and placebo groups on day 240.

■ COMMENTARY

MSC therapy has been studied and found to be beneficial in animal and laboratory models of several neurodegenerative diseases including amyotrophic lateral sclerosis, Parkinson's disease, Friedreich's ataxia, and Huntington disease. The exact mechanism of action of MSC in neurodegeneration is not known, but it is proposed to possibly modulate neuroinflammatory and apoptotic processes, decrease glutamate excitotoxicity, or improve deficiency of various growth factors. The delivery of MSC to the brain might be compromised by the blood brain barrier. However, this barrier might be less intact in the multiple system atrophy than in normal subjects. The authors chose both intra-arterial and intravenous routes for infusions of the MSC, although the latter is more inferior because of entrapment of the stem cells in solid organs. The intra-arterial infusion in turn may result in ischemic lesions in the brain as evidenced by the adverse effects profile observed in the study. Overall, the investigators met their primary endpoint of a statistically significant difference in the UMSARS scores, along with observed positive results in secondary endpoints such as glucose metabolism, cortical density, and cognitive scores. The authors recognized the limitations of this study, which include the relatively small number of subjects, only mild and moderate stages of the disease, and inclusion of only MSA-C patients. Moreover, the safety of intra-arterial infusions is of concern given the significant percentage of patients developing ischemic lesions seen on the MRI, even though they are likely asymptomatic. The most significant difference in the treatment effect was observed at day 240, after which the patients who received stem cell treatment seemed to have worsened at a slightly higher rate than placebo patients, but retained some improvement in the UMSARS scores at the end of the study (360 days). This might present a need for repeated infusions which in turn could result in accumulative ischemic burden to the patients, thus presenting unacceptable risk. However, the study did demonstrate evidence of a possible neuroprotective effect of the mesenchymal stem cells. Therefore, a repeat multicenter trial with patients of all types of multiple system atrophy would be warranted when the safety concerns of the MSC delivery system are addressed. ■

Reference

1. Lee PH, et al. Autologous mesenchymal stem cell therapy delays the progression of neurological deficits in patients with multiple system atrophy. *Clin Pharmacol Ther* 2008;83:723-730.

CME Objectives

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

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

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
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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 childhood epilepsy is *not* true?

a. Most children with drug resistance present with focal epilepsy syndromes.

b. Idiopathic/cryptogenic forms are more likely to have long-term remissions.

c. Most patients with secondary/structural lesions do not become seizure-free.

d. Pharmacoresistant secondary epilepsies should be considered for surgery.

e. Post-traumatic secondary epilepsy has a good prognosis.

2. Antioxidants have been shown to be beneficial in animal models of neurodegenerative diseases.

a. True

b. False

3. Which of the following agents has been shown to be beneficial in the treatment of polymyositis in controlled trials?

a. Corticosteroids

b. Azathioprine

c. Methotrexate

d. Mycophenolate mofetil

e. Intravenous immunoglobulin

4. Mild cognitive impairment in Parkinson's disease (MCI-PD) is characterized by which of the following?

a. MCI-PD occurs only in advanced Parkinson's disease.

b. Cortical but not subcortical network abnormalities are demonstrated by fMRI.

c. Only subcortical and not cortical network abnormalities are demonstrated by fMRI.

d. Ligands detected by SPECT measuring dopamine transporter density demonstrate striatal abnormalities in PD-MCI over and above those in PD alone.

5. Increased intracranial pressure with loss of complexity after traumatic brain injury predicts poor long-term prognosis.

a. True

b. False

6. Mesenchymal stem cell infusions via the intra-arterial route may cause ischemic strokes as a complication.

a. True

b. False

In Future Issues:

The Latest in Migraine Treatment

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.*

Does Finasteride Cause Permanent Sexual Side Effects?

In this issue: Side effects of finasteride; new ruling on pharmaceutical companies paying generic manufacturers; and FDA actions.

Sexual side effects of finasteride

Finasteride — the popular drug used to treat male pattern baldness and symptomatic benign prostatic hypertrophy — may cause long-term sexual dysfunction, according to a new study. Several recent studies have shown that the drug, which is marketed as 1 mg (Propecia) and 5 mg (Proscar), can cause sexual side effects that persist after stopping the drug in as many as 20% of men. In April, the FDA required new labeling for both strengths regarding libido, ejaculation, orgasm disorders, and even infertility that may persist after treatment ends. The new study looked at 54 men, with an average age of 31, who reported ≥ 3 months of sexual side effects after taking the 1 mg strength for male pattern baldness. All men were previously healthy without previous history of sexual dysfunction, medical conditions, psychiatric conditions, or prescription medication use. After 9-16 months of follow-up, 96% of subjects reported persistent sexual side effects (based on the Arizona Sexual Experience Scale). The duration of finasteride use did not correlate with changes in sexual dysfunction scores. The authors urge prescribers of finasteride to warn men of potential adverse effects (*J Sex Med* published online July 12, 2012). ■

Pharmaceutical company ruling

Is it legal for pharmaceutical companies to pay generic manufacturers to keep their products off the market? Until now it has been. Brand-name manufacturers have written enormous checks to keep their low-cost generic competitors off the market. That may change, however, after a federal appeals court in Philadelphia ruled that the practice is anticompetitive, a decision that is counter to three previous federal circuit courts rulings. *The New York Times* cites the example of Bayer Pharmaceuticals which paid generic drug maker Barr Laboratories and other generic houses $400 million to withhold their generic version of ciprofloxacin, their $1 billion a year blockbuster antibiotic. The case could eventually end up at the Supreme Court. At stake is billions of dollars in lost profits for pharmaceutical manufacturers, but an equal amount of savings for Medicare/Medicaid, health plans, and consumers. ■

FDA actions

The FDA has approved the second new weight-loss medication within a month. The new product combines phentermine along with topiramate in an extended-release product. Phentermine has been marketed since 1959 and was part of the infamous "fen-phen" combination that was popular in the 1990s (fenfluramine was eventually banned due to cardiac valvulopathy in 1997). Topiramate is currently marketed as an anticonvulsant and for migraine prophylaxis as Topamax. The combination was rejected by the

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FDA in 2010 due to safety concerns, but Vivus Pharmaceuticals submitted additional data to the agency and recently won approval in July. In the process, the company changed the brand name from Qnexa to Qsymia. Similar to the recently approved lorcaserin (Belviq), phentermine/topiramate is approved as an addition to a reduced-calorie diet and exercise for weight management in adults with a BMI of 30 or greater, or with a BMI of 27 or greater with at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia. In two placebo-controlled trials, 3700 obese and overweight patients lost an average of 6.7-8.9% of their body weight, depending on the recommended or higher dose therapy (slightly better results than those seen with lorcaserin). Patients who have not lost at least 3% of their body weight by week 12 should discontinue the drug. Because of continued safety concerns, the drug was approved with a Risk Evaluation and Mitigation Strategy (REMS), which consists of a medication guide, prescriber training, and pharmacy certification. The drug cannot be used during pregnancy or in patients with recent stroke or heart disease, and patients should have their heart rates monitored during therapy. Vivus will market Qsymia immediately, but will be required to conduct 10 postmarketing studies to assess safety.

The FDA has approved aclidinium bromide, a dry powder inhaler for long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). Aclidinium is a long-acting antimuscarinic agent that works primarily on the M3 receptor causing sustained bronchodilation. The approval was based on three studies of nearly 1300 patients with COPD. The drug may cause anticholinergic side effects, including worsening narrowing-angle glaucoma and urinary retention. It should not be used as a rescue inhaler and is not recommended for those 18 years of age or younger. It is dosed twice a day. Aclidinium inhaler is the second anticholinergic inhaler to be approved after tiotropium (Spiriva), which was approved in 2004. Aclidinium will be distributed by Forest Laboratories and will be marketed as Tudorza Pressair.

The FDA has approved mirabegron to treat adults with overactive bladder. The drug is a novel, once-daily beta-3 adrenergic agonist that works by enhancing storage function and relaxing the urinary bladder, a unique effect and distinct from currently marketed antimuscarinics that inhibit bladder contraction. The once-a-day medication will be available in 25 mg pills. The dose can be increased to 50 mg after 2 months if needed. The approval was based on three placebo-controlled trials that showed statistically significant improvement in incontinence episodes and number of urinations per 24 hours. The most common adverse effects were hypertension, nasopharyngitis, urinary tract infection, and headache. Mirabegron will be marketed by Astellas Pharma as Myrbetriq.

The FDA has approved a new colon cleansing agent for colonoscopy prep. The new prep is sodium picosulfate, magnesium oxide, and citric acid in powder form that is dissolved in water and taken in two doses the night before and the morning of the procedure. It may also be taken the afternoon and the evening before the procedure (Day-Before regimen). The safety and efficacy of the new agent was studied in two studies of about 1200 patients undergoing colonoscopy in which standard PEG plus electrolytes was used as a comparator, and the new prep was found to be at least as effective as the standard prep. Ferring Pharmaceuticals will market the new two-dose prep as Prepopik.

The FDA has approved icosapent ethyl, a new fish oil preparation for the treatment of hypertriglyceridemia. It is approved as an adjunct to diet to treat patients with triglyceride levels greater than 500 mg/dL. The drug contains ultra purified ethyl EPA, an omega-3 fatty acid. The new product follows GlaxoSmithKline's Lovaza, another fish oil that is currently marketed for the same indication and generates more than $1 billion in annual sales. The new product is manufactured by Amarin Corporation and will be marketed as Vascepa. Fish oils are effective at lowering triglycerides but evidence is lacking that they are effective for secondary prevention of cardiovascular disease (*Arch Intern Med* 2012;172:686-694).

An FDA advisory committee has recommended an new indication for Genentech's ranibizumab (Lucentis) for the treatment of diabetic macular edema, an indication for which there is currently no approved therapy. The drug is approved to treat neovascular age-related macular degeneration and macular edema following retinal vein occlusion. Diabetic macular edema is commonly treated with laser therapy, a procedure that has the potential side effect of some vision loss. The FDA generally follows its advisory committee's recommendations and should make a final recommendation later this year. ■

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By Louis Kuritzky, MD

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Risk for Zoster from the Vaccine in Immunosuppressed Persons

Source: Zhang J, et al. *JAMA* 2012;308: 43-49.

THE PREVAILING WISDOM SUGGESTS THAT because herpes zoster vaccine (ZOS) is a live virus, it should not be administered to persons receiving immunosuppressive treatments, such as biologic agents or methotrexate for rheumatoid arthritis, or chronic prednisone therapy of 20 mg/d or more. The concern is that instead of mounting an immune response to the vaccine, vaccinees might actually experience a case of shingles as a result of the vaccine.

To examine the real-life risk of an acute zoster infection after ZOS, a retrospective analysis was performed on a large Medicare database (n = 463,541) of persons with a diagnosis of rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease. Any one of these disorders would be commonly treated with immunosuppressive agents, corticosteroids, or both.

The analysis looked at the number of cases of shingles within 42 days of ZOS, anticipating that if the live virus vaccine had induced shingles, it should certainly have happened within that 6-week window after vaccination.

No increased incidence of shingles was seen in ZOS recipients, even in patients on biologics. Indeed, ZOS was associated with a 39% lower risk of shingles during the 42-day window of observation, and a reduced risk during the subsequent 2 years (median) of follow-up. ZOS appears to be beneficial even in immunocompromised individuals, and the authors challenge the propriety of current recommendations that advise against ZOS administration in such populations. ■

Cerebral Aneurysms: What's in Your Patient's Future?

Source: UCAS Japan Investigators. *N Engl J Med* 2012;366:2474-2482.

THE UCAS (UNRUPTURED CEREBRAL ANeurysm) Japan study began enrolling patients with incidentally discovered cerebral aneurysms (CRAs) for an observational study in 2001. The primary purpose of the study was to better delineate the natural history of incidentally discovered CRAs (as opposed to discovery through neurologic signs or symptoms). Prior to this trial, it had been generally recognized that CRAs < 7 mm rarely rupture, and that posterior circulation CRAs have a greater risk than anterior.

This prospective cohort study included patients (n = 6413) with incidentally discovered CRA and minimal, if any, disability. Subjects were followed for up to 8 years. During this interval, the annual rate of CRA rupture was approximately 1%. When rupture did occur, it was fatal in 35% of cases, or led to moderate-severe disability in another 29%.

The most important predictive factors for rupture were size of the CRA, age, and gender (females are at greater risk). For example, when compared with lesions < 7 mm, a 7-9 mm lesion had a three-fold increase of rupture, and a lesion > 10 mm had a nine-fold increased risk. Risk in women was 1½ times as great as men, and persons over age 70 were 21% more likely to experience aneurysm rupture. Because the entire population of enrollees was Japanese, the generalizability of these results may have limitations, but nonetheless provide perhaps the most accurate mapping of risk factors for rupture of CRAs. ■

Elucidating the 'Best' Interval for Bone Density Screening in Osteoporosis

Source: Yu EW, Finkelstein JS. *JAMA* 2012;307:2591-2592.

ONCE A BASELINE BONE MINERAL DENSITY (BMD) has been obtained, it is unclear when the study should be repeated. For one thing, the literature suggests that only about 30% of bone strength may be attributable to bone density. Additionally, some of the interventional trials using bisphosphonates have found fracture reduction despite continuation of bone density *loss* over the first year or two of intervention. Finally, the rate at which BMD declines has been linked to the baseline BMD.

For instance, a study that looked at menopausal women (age > 67 years) for progression of BMD loss found some fairly startling results: It would take approximately 15 years for 10% of women with normal baseline BMD (T score < -1.5) to incur sufficient loss of BMD to cross the diagnostic threshold for osteoporosis (T score < -2.5). Similarly, for women with osteopenia (T score -1.5 to -2.0) at baseline, it would require 5 years for 10% of

them to progress to frank osteoporosis. At the greatest level of osteopenia (T score -2.0 to -2.5), progression to osteoporosis in 10% of women would be expected to occur within 1 year. These projections assume no addition of new risk factors known to accelerate bone loss.

Although it is tempting to get BMD more often, it may not be helpful. Although the data are sufficiently uncertain that the USPSTF has been unable to provide confirmation of a preferred schedule, Yu et al suggest following rescreening intervals for postmenopausal women: for women with normal BMD at baseline, 10 years; for women with mild osteopenia and low FRAX score at baseline, 5-10 years; for women with moderate osteopenia or FRAX score approaching treatment threshold, 2 years. ■

An Unexpected Connection Between PTSD, ACE Inhibitors, and ARBs

Source: Khoury NM, et al. *J Clin Psychiatry* 2012;73:849-855.

Several lines of evidence suggest that modulation of the renin-angiotensin-aldosterone system with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) might potentially have positive effects on post-traumatic stress disorder (PTSD). Preclinical data indicate favorable cerebral effects of ARBs, such as stress reduction and anxiolysis. Some ARB trials have reported positive effects on cognition, quality of life, and depression or anxiety.

Khoury et al performed a cross-sectional observational data analysis of PTSD patients (n = 505) comparing symptoms in those who were being treated with an ARB/ACE vs controls (no ARB/ACE treatment). Overall, PTSD symptom scores were almost 25% lower among patients treated with ACE or ARB therapy ($P = 0.04$).

The better symptom scores among PTSD patients treated with ARB or ACE therapy were not simply due to the fact that hypertension (which is more common in PTSD patients) was treated; no other antihypertensive medications (e.g., calcium channel blockers, diuretics, beta-blockers) were found to have similar favorable effects.

The mechanism through which ACE/ARB treatments impact PTSD is not well established, but may be through modulation of the noradrenergic system. ■

The Right Amount of Vitamin D to Prevent Fractures

Source: Bischoff-Ferrari HA, et al. *N Engl J Med* 2012;367:40-49.

Inclusion of vitamin D (VTD) in the regimen for fracture prevention is time honored and condoned by major guidelines. Intuitively, VTD should be helpful, but the analyses of data in reference to this topic are mixed. For instance, although one meta-analysis indicated an 18% reduction in hip fracture if a minimum of 482 IU/d VTD was prescribed, equally prominent data concluded that VTD alone was of *no benefit*. So, how about further investigation of the subject?

Bischoff-Ferrari et al performed an analysis on 11 double-blind, randomized, controlled trials of oral VTD supplementation (n = 31,022) seeking to determine if supplementation (with or without calcium) reduced hip fracture. According to their analysis, there was no statistically significant reduction in fracture risk in subjects assigned to VTD. Story over? Well, maybe not quite.

First, although hip fracture was not reduced, there was a marginally statistically significant 7% reduction of total non-vertebral fractures. Additionally, when analyzed from the viewpoint of the *actual intake* of VTD instead of what subjects were assigned to, the picture looks quite different. Specifically, subjects in the highest quartile of actual VTD intake (prescribed supplementation plus dietary intake) enjoyed a statistically significant 30% reduction in hip fracture. For the time being, at least 800 IU/d VTD supplementation is recommended in persons ≥ age 65. ■

Prevention of Diabetes

Source: Perreault L, et al. *Lancet* 2012; 379:2243-2251.

It appears that one's ounce of prevention may have to be weighed more carefully to attain the fullest pound of cure. Why? The answer lies in subgroup analysis of recent trials in diabetes prevention.

There have been many diabetes prevention trials, essentially all of which have been successful to a varying degree. Overall, diet and exercise appear to be as efficacious as any other intervention. Pharmacologically, numerous classes of agents have been successfully tried (metformin, thiazolidinedione, alpha-glucosidase inhibitor, etc.). What has been learned is that successful incorporation of diet/exercise or pharmacotherapy over a 4- to 6-year period reduces the likelihood of progressing from prediabetes to diabetes (typically, 6-10%/year) by half or more. But there is more to the story.

After successful treatment (pharmacotherapy or lifestyle), the majority of those who are prevented from progressing to frank diabetes still fulfill criteria for prediabetes (A1c 5.7-6.4). Between 20-50% of treated subjects are restored to currently recognized normal glucose levels.

The analysis by Perrault et al indicates that persons with prediabetes in whom normal glucose homeostasis was restored are half as likely to progress to frank diabetes over a 3-year, post-trial observation period as individuals whose glucose control was improved, but still reflected prediabetes. Striving for the best glucose control in prediabetes may have long-term benefits. ■

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