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INSIDE

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What Would You Do, Doc?

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

Clinical Assistant Professor, West Virginia University School of Medicine, Charleston, WV

Dr. Gupta reports no financial relationship relevant to this field of study.

Synopsis: *Physicians often do not choose the same clinical treatments for themselves as they would recommend to their patients.*

Source: Ubel PA, et al. Physicians recommend different treatments for patients than they would choose for themselves. *Arch Intern Med* 2011; 171:630-634.

In clinical practice, one of the most challenging situations arises when our patients facing difficult decisions themselves ask the physician, "What would you do, doc?" From the patient's perspective, it is only natural when faced with such often complex treatment decisions to turn to the one person who has already guided them so far — the physician. Conversely, most physicians are pleased to discuss treatment options in detail along with the available evidence and address the patient's concerns. However, most still stop short of making a clear recommendation for a particular treatment option. Most physicians understand that their recommendations can lead people to make decisions that could go against what the patient may otherwise prefer.[1] Therefore, understanding that their advice might influence patients' decisions away from the preferred treatment option, physicians often encourage their patients to identify their own preferences and help to find the treatment option most consistent with them.[2] Yet, as more treatment options become available, the decision matrix becomes more complex resulting in more dependence on the physician to assist in decision making.[3,4] In the face of this rising dependence on the physician in the shared decision-making process, little is known about when physicians do make such a recommendation, what shapes this advice? And, does the very act of making such a recommendation influence how physicians judge treatments?

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In their study, Ubel et al tested whether making a recommendation changes the way that physicians think about medical decisions. The researchers conducted two randomized experiments in which they provided two alternatives each and asked physicians to decide which treatment they would choose if they themselves were the patient or which treatment they would recommend to a patient facing the same decision. In the first experiment, 500 physicians were asked to imagine that either they or one of their patients had just received a diagnosis of colon cancer and faced a choice of one of two operations to treat the cancer. Both surgeries cured the colon cancer in 80% of patients, however, one surgery had a higher mortality rate, but fewer adverse effects, whereas the second surgery had a lower mortality rate but a small percentage of patients experienced colostomy, chronic diarrhea, intermittent bowel obstruction, or a wound infection. This choice involved a trade-off between the risk of death and the chance of one of the four surgical complications mentioned. Of the 242 physicians who responded to the questionnaire, 37.8% of physicians chose the surgical procedure with a higher rate of death, but a lower rate of adverse effects. In comparison, when asked to make a recommendation for a patient, only 24.5% of physicians chose this option.

The second experiment involved surveying 1,600 physicians about a new strain of avian influenza that had just arrived in the United States. One group of physicians was asked to imagine that they had been infected and the other group was asked to imagine that his or her patient was infected. Without the treatment (immunoglobulin therapy), infected patients would have a 10% death rate and a 30% hospitalization rate with an average stay of 1 week. With treatment, the rate of adverse events would be reduced by half; however, it would also cause death in 1% of patients and permanent neurological paralysis in 4% of patients. Of the 698 physicians who responded, 62.9% chose to forgo immunoglobulin treatment when imagining they had been infected to avoid its adverse effects. However, when imagining that a patient had been infected, only 48.5% of physicians recommended not getting the treatment. Further analysis demonstrated that choice was not associated with respondent age, sex, or volume of patient care.

Overall, physicians were more likely to choose the treatment with the greatest chance of survival when recommending a treatment for their patients, but more likely to choose the treatment with the lowest risk of side effects or complications for themselves.

■ COMMENTARY

While this study doesn't suggest that physicians always make better decisions for others than they would make for themselves or vice versa, it is an interesting insight into the physicians' ability to make a distinction when making treatment recommendations vs when making a treatment decision for themselves. Perhaps some of this can be explained by the fact that we are taught not to make value judgment for others in the process of rendering care. Therefore, we may not be able to fully engage the same criteria and biases for others (patients) as we would for ourselves. In other words, physicians in this study may have been able to make more candid treatment decisions for themselves since they did not feel the need or the fear to explain those decisions to anyone. However, by the same argument, the question then arises whether the need to defend recommendations for patients interferes with certain inherent biases in the physicians' ability to make guileless treatment recommendations. It is critical to pursue more research in this field to learn what biases play a role when physicians and other health care professionals make recommendations. Understanding the roots of such biases can help physicians and patients make decisions that best reflect each patient's values regarding his or her medical condition. After all, it's not about making the right or the wrong treatment recommendation, it's about making the best decision for each individual patient! ■

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CRP in Acute Pericarditis

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

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Dr. Crawford serves on the speakers bureau for AstraZeneca.

This article originally appeared in the May issue of Clinical Cardiology Alert. *At that time it was peer reviewed by Ethan Weiss, MD, Associate Professor of Medicine, Division of Cardiology, University of California, San Francisco, CA. Dr. Weiss is an advisory board member for Bionovo.*

Synopsis: *High sensitivity C-reactive protein may be useful in acute viral or idiopathic pericarditis for establishing the diagnosis, determining the duration of therapy, and suggesting when to escalate therapy.*

Source: Imazio M, et al. Prevalence of C-reactive protein elevation and time course of normalization in acute pericarditis. Implication for the diagnosis, therapy and prognosis of pericarditis. *Circulation* 2011;123:1092-1097.

THE UTILITY OF INFLAMMATORY MARKERS IN ACUTE PERICARDITIS is not well understood. Thus, these investigators from Italy prospectively evaluated serial high sensitivity C-reactive protein (hs-CRP) serum levels in patients with acute pericarditis followed for 24 months on average. Of the 240 cases diagnosed as acute pericarditis, 200 had idiopathic (152) or viral (48) pericarditis and are the subjects of this report. Hs-CRP testing was done at presentation and every week until normalization. Values > 3.0 mg/L were considered elevated. All patients received empirical anti-inflammatory therapy: aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) in 170; colchicine in 100; and corticosteroids in 30. Drug therapy was usually tapered in 3 to 4 weeks. Symptom persistence at 1 week, recurrent cardiac tamponade, and constrictive pericarditis were considered adverse events. Patients ranged in age from 18 to 90 years old (mean 53) and about 50% were female. All presented with chest pain, about 85% had diagnostic ECG changes, about one-third had pericardial rubs, and about 50% had pericardial effusions. At presentation, 78% had elevated hs-CRP, which steadily declined to 5% at 3 weeks and none at 4 weeks. Negative hs-CRP values on presentation may have been due to early presentation (15 of 44) or previous anti-inflammatory therapy (22 of 44). A normal hs-CRP value at 1 week was highly predictive of a recurrence free survival ($P < 0.001$). An incomplete response to initial anti-inflammatory therapy and the use of corticosteroids also were independent predictors of recurrence. The authors concluded that hs-CRP is elevated in three quarters of patients with acute pericarditis and serial measurements identify patients at higher risk of recurrence.

■ COMMENTARY

This prospective observational study of patients with acute idiopathic or viral pericarditis is an important contribution because it suggests a procedure for managing these patients. They clearly identify acute pericarditis clinically as patients who have two of the following four criteria: chest pain consistent with pericarditis; a friction rub; diagnostic ECG changes; or a pericardial effusion on echocardiography. They find that hs-CRP is elevated in three-fourths of them and persistently negative in 3.5%. However, there is no control group of patients with chest pain, but no evidence of pericarditis to determine the false-positive rate. Thus, it is not an absolute diagnostic criterion, but if elevated does support the diagnosis.

Current therapy for acute idiopathic or viral pericarditis is empiric. Acute inflammatory agents are currently given until the pain resolves or for some predetermined interval. Hs-CRP offers a more informed approach. The authors suggest weekly values with full dose initial therapy continuing until hs-CRP is < 3.0 mg/L; then tapering therapy off. Of course this would be modified if the patient does not improve symptomatically or there is evidence of recurrence.

Their experience supports previous observational results on the course of treated acute pericarditis. About one-third had persistent symptoms at one week and about one-third had a recurrence during follow up. Only 2% developed pericardial tamponade and none developed constriction over a 2 year average follow-up. These data confirm the relatively benign prognosis of idiopathic or viral acute pericarditis with the biggest problem being recurrence. In this study there were three independent predictors of recurrence: incomplete response to therapy at one week, use of corticosteroids, and an elevated hs-CRP at one week. These observations confirm that corticosteroids should not be used as first-line therapy, but reserved for refractory cases. In my experience, using colchicine for those who do not improve quickly on NSAIDs has almost eliminated the need for corticosteroids. In the future, I will use hs-CRP to tailor the duration of therapy. ■

Text is Best? Cell Phone Use and Brain Changes

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

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Dr. Greenfield reports no financial relationship relevant to this field of study.

This article originally appeared in the April issue of Alternative Medicine Alert. *At that time it was peer reviewed by David Kiefer, MD, Clinical Instructor, Family Medicine, University of Washington, Seattle, Clinical Assistant Professor of Medicine, University of Arizona, Tucson, Adjunct Faculty, Bastyr University, Seattle. Dr. Kiefer reports no financial relationship relevant to this field of study.*

Synopsis: *A small study of the effects of acute cell phone use on brain glucose metabolism revealed significant increases in areas near the location of a phone's antenna. The findings do not imply that cell phone use causes brain damage, only that the electromagnetic fields from them do cause changes in brain function.*

Source: Volkow ND, et al. Effects of cell phone radiofrequency signal exposure on brain glucose metabolism. *JAMA* 2011;305:808-814.

Cell phone use around the globe has exploded, but not without some concerns for health and safety. Epidemiologic and human clinical studies into the effects of radiofrequency-modulated electromagnetic field (RF-EMF) exposure from cell phones have produced variable results, but it is known that these RF-EMFs are absorbed in the brain, and while the intensity of cell phone RF-EMFs is low they may still interfere with neuronal activity. The lack of clear answers regarding the impact of cell phone use on brain function and risk of malignancy apparently prompted the authors of this randomized crossover trial to further investigate the effect of acute active cell phone exposure. In particular, they focused on regional brain glucose metabolism, a marker of brain activity, as measured using PET with injection of (18F) fluorodeoxyglucose (18FDG).

Healthy subjects (n = 47) were recruited through local advertisements and screened for the absence of medical, psychiatric, or neurologic diseases. Special attention was given to ensure that participants did not abuse addictive substances (including alcohol, psychoactive drugs, and nicotine). Participants each received $250 for their participation in the study.

Cell phones were placed over each ear with microphones directed toward the participant's mouth and were secured to the head using a muffler that did not interfere with the lower part of the cell phone (where the antenna is located). All participants had two scans performed on separate days using PET with 18FDG injection. For one of the days both cell phones were turned off, while on the other day the right cell phone was both activated and receiving a call consisting of recorded text (sound was muted to avoid confounding from auditory stimulation) and the left cell phone was off. The order of conditions was randomly assigned, and participants were blinded to the condition. The mean time between the two studies was 5 days.

Activation of the right cell phone was started 20 minutes prior to 18FDG injection and maintained for 30 minutes afterward to correspond with the 18FDG uptake period. During the 50-minute session participants sat on a comfortable chair in a quiet, dimly lit room with their eyes open. A nurse was present to ensure that they kept their eyes open and did not fall asleep. At the end of the sessions, the cell phones were removed and the participants were positioned in the PET scanner.

Statistical parametric mapping was used to determine the main outcome measure of brain glucose metabolism computed as absolute metabolism (mmol/100 g per minute) and as normalized metabolism (region/whole brain).

Whole-brain glucose metabolism did not differ between conditions, which for the "off" condition corresponded to 41.2 mmol/100 g per minute (95% confidence interval [CI], 39.5-42.8) and for the on condition to 41.7 mmol/100 g per minute (95% CI, 40.1-43.3). Regional effects were significant. Specifically, comparisons on absolute metabolic measures showed significant increases (35.7 vs 33.3 mmol/100 g per minute for the "on" vs "off" conditions, respectively; mean difference, 2.4 [95% CI, 0.67-4.2]; $P = 0.004$) in a region that included the right orbitofrontal cortex and the lower part of the right superior temporal gyrus. No areas showed decreases. Similar results were obtained for the analysis of normalized metabolic images (normalized to whole-brain glucose metabolism), which also showed significant increases (1.048 vs 0.997 for the on vs off conditions, respectively; mean difference, 0.051 [95% CI, 0.017-0.091]; $P < 0.001$) in a region that included right orbitofrontal cortex and right superior temporal gyrus. Increases in brain glucose metabolism were significantly correlated with the estimated electromagnetic field amplitudes both for absolute metabolism ($R = 0.95$, $P < 0.001$) and normalized metabolism ($R = 0.89$; $P < 0.001$).

The researchers concluded that the human brain is sensitive to the effects of RF-EMFs from acute cell phone exposures. The findings of increased brain glucose metabolism in regions closest to the antenna during acute cell phone exposure suggest that brain absorption of RF-EMFs may enhance the excitability of brain tissue. They also note that this finding is of as yet unknown clinical significance.

■ **COMMENTARY**

The media pounces on stories about EMFs and possible health risks, and in at least one sense for good reason — we're surrounded by them. On the other hand, there seems little we can do about it, and the stories often do little more than get us anxious. Perhaps the stories around cell phone use are different, however.

There have long been questions about the safety of prolonged exposure to EMFs, especially as relates to the development of malignancy, including cell phone use. Existing studies have left salient questions largely unanswered except to say it's probably best to use an earpiece and microphone rather than hold the phone to your ear. The present study adds fuel to that recommendation, but remains speculative.

Brain exposure to EMFs from cell phones appears to be well localized in the area of the antennae and to result in increased brain metabolic activity. The mechanisms by which this occurs have yet to be identified but may include changes in ion flux and cell membrane permeability. Even disruption of the blood-brain barrier has been posited. Beyond these hypotheses, however, lies an even greater question: How relevant are the findings? The study authors are careful to point out that their findings do not in and of themselves suggest there is damage to the brain as a result of the changes identified with acute RF-EMF exposure, only that changes do occur.

Although a small study, it raises questions about cell phone safety that need to be addressed. Until we know more, it seems prudent to recommend that our patients use headsets rather than holding the phone against their ears for long conversations. ■

Brief Reports

The Benefits of Broader Exposure

By Carol A. Kemper, MD, FACP

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Dr. Kemper does research for Abbott Laboratories and Merck.

This article originally appeared in the April issue of Infectious Disease Alert. *At that time it was peer reviewed by Timothy Jenkins, MD, Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Jenkins reports no financial relationship to this field of study.*

Source: Ege MJ, et al. Exposure to environmental microorganisms and childhood asthma. *N Engl J Med* 2011;364:701-709.

It has been speculated that children growing up in an overly clean, suburban environment may experience greater atopy and asthma than children growing up in the inner city or on a farm. These investigators report on the results obtained from two large-scale cross-sectional studies, performed in Europe, comparing the prevalence of atopy and asthma in children. The first study focused on 6963 children of farmers and school-aged children (ages 6-13 years) growing up in largely rural areas of central Europe; 52% lived on a farm; and 8% had a diagnosis of asthma. Dust from the children's mattresses were collected and DNA extractions were performed. The second study focused on a stratified random sample of 3668 school-aged children (ages 6-12 years) living in central Europe. Only 16% of these children lived on farms and 11% of these children had a diagnosis of asthma. Airborne dust samples were collected from the children's bedrooms for 2 weeks.

Both studies revealed that the risk of asthma was inversely related to the diversity of microbial exposure in the children's bedroom environment, independent of whether they lived on a farm. In addition, the presence of a more circumscribed range of exposure to a few organisms was also inversely related to an increased risk of asthma. Attempts to create a statistically relevant diversity score, either by a factor analysis or by summing the total exposure, demonstrated that diversity of flora, however it was measured, was significantly less in children with asthma (but not atopy).

Several "zones" identified in the factor analysis suggested that exposure to groups of bacteria and fungi were associated with a protective effect, although no single organism could be identified as protective. In addition, exposure to fungal taxon eurotium and penicillium seemed to have a protective effect. ■

Dementia Occurs in Approximately 20% of Patients After a First Stroke

By Matthew E. Fink, MD

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Dr. Fink reports no financial relationship to this field of study.

This article originally appeared in the April issue of Neurology Alert. *At that time it was peer reviewed by M. Flint Beal, MD, Anne Parrish Titzel Professor, Department of Neurology and Neuroscience, Weill Cornell Medical Center, New York, NY. Dr. Beal reports no financial relationship to this field of study.*

Source: Bejot Y, et al. Prevalence of early dementia after first-ever stroke. A 24-year population-based study. *Stroke* 2011; 42:607-612.

From 1985 to 2008, all first-ever strokes in the city of Dijon, France (150,000 inhabitants) were recorded,

and among those patients who were testable (3201/3948 or 81%), 20.4% had post-stroke dementia. The prevalence of post-stroke dementia in patients with lacunar disease was 7 times higher than in patients with intracerebral hemorrhage. Age, vascular risk factors, presence of hemiplegia, and use of prestroke antiplatelet medications were associated with an increased prevalence of post-stroke dementia. ■

Lowering Blood Pressure Reduces Hematoma Growth After Acute Intracerebral Hemorrhage

By Matthew E. Fink, MD

Source: Arima H, et al, for the Intensive Blood Pressure Reduction in Acute Cerebral hemorrhage Trial (INTERACT) Investigators. Lower treatment blood pressure is associated with greatest reduction in hematoma growth after acute intracerebral hemorrhage. *Hypertension* 2010;56:852-858.

INTERACT included 404 patients with acute intracerebral hemorrhage (ICH), elevated systolic blood pressure (BP) (150 to 220 mmHg), and capacity to lower BP within 6 hours of onset. CT was performed at baseline and at 24 hours to compare hematoma size. There was no significant association between baseline systolic BP levels and hematoma volume. Maximum reduction in hematoma growth occurred in the one-third of patients with the lowest on-treatment systolic BP levels (median = 135 mmHg). Intensive BP reduction to systolic levels between 130 and 140 mm Hg is likely to provide maximum protection against hematoma growth. ■

Pharmacology Update

Gabapentin Enacarbil Extended-Release Tablets (Horizant™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationship to this field of study.

A PRODRUG OF GABAPENTIN HAS BEEN APPROVED BY THE FDA for the treatment of restless legs syndrome (RLS). This is the first nondopaminergic drug approved for this indication. Gabapentin enacarbil is licensed from XenoPort, Inc., and marketed by GlaxoSmithKline as Horizant.

Indications

Gabapentin enacarbil is indicated for the treatment of moderate-to-severe primary RLS in adults.[1]

Dosage

The recommended dose is 600 mg once daily taken with food around 5 p.m.[1] If the dose was not taken at the appropriate time, the next dose should be taken the following day. The tablet should be taken whole and not cut, crushed, or chewed.

Gabapentin enacarbil is available as 600 mg extended-release tablets.

Potential Advantages

Gabapentin enacarbil has a different side effects profile compared to dopaminergic drugs such as ropinirole and pramipexole. It has not been associated with rebound and augmentation.

Potential Disadvantages

The most frequently reported adverse effects (compared to placebo) were somnolence or sedation (20% vs 6%) and dizziness (13% vs 4%).[1] As with antiepileptic drugs, gabapentin enacarbil may increase the risk of suicidal behavior and ideation.[1] Patients should be monitored for this as well as emergence or worsening of depression and/or any changes in mood or behavior.

Comments

Gabapentin enacarbil provides improved absorption compared to gabapentin. Food further enhances the absorption. The efficacy and safety of gabapentin enacarbil was studied in two 12-week clinical trials in adults with RLS.[1,2] The primary efficacy endpoints were the International Restless Legs Syndrome (IRLS) Rating Scale and Clinical Global Impression of Improvement (CGI-I) scores. The IRLS Rating Scale contains 10 items with a range of scores from 0 to 40 that assess the severity of sensory and motor symptoms, sleep disturbance, daytime somnolence/sedation, and impact on activities of daily living and mood associated with RLS. CGI-I Scale is the investigators assessment of the patient's overall change in RLS symptoms from baseline. Those categorized as "much improved" or "very much improved" at 12 weeks are defined as responders. In Study 1, patients with IRLS of 15 or higher were randomized to 1200 mg of gabapentin enacarbil (n = 112) once daily at 5 p.m. or placebo (n = 108). In Study 2, they were randomized to 600 mg (n =

114), 1200 mg (n = 111), or placebo (n = 96). The mean changes in IRLS Scores in Study 1 were -13.2 for 1200 mg and -8.0 for placebo with response rates 76% and 39%, respectively. Results for Study 2 were -13.8 (600 mg), -13.0 (1200 mg), and -9.8 (placebo). The response rates were 73%, 77%, and 45%, respectively. The higher dose, 1200 mg, did not offer any added benefit over the 600 mg dose but was associated with a higher incidence of side effects. The most frequently reported adverse events were somnolence and dizziness. Efficacy was detected as early as week 1. Results from an open-label study indicate that the improvement was maintained for up to 64 weeks.[3] There are currently no published comparative trials between gabapentin enacarbil and a dopaminergic agent. However, the magnitude of the changes in RLS scores was similar to those reported for ropinirole and pramipexole.[4,5] Rebound and augmentation in RLS have not been reported with gabapentin. On the other hand, increased risk of suicidal behavior and ideation has been associated with gabapentin.

Clinical Implications

RLS is characterized by an urge to move the legs with or without an actual paresthesia, worsening of symptoms with inactivity, improvement with activity, and worsening of symptoms in the evening and at night.[6] Currently, dopamineric agents (e.g., ropinirole, pramipexole) are FDA-approved treatments. With chronic therapy, patients may develop rebound or augmentation of their condition. Gabapentin provides an alternative that appears not to cause worsening of symptoms. ■

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CME Questions

27. In the study by Ubel et al, when physicians make treatment decisions for themselves compared with making treatment recommendations for their patients, they:

a. make similar decisions.
b. make better decisions for themselves than for their patients.
c. make better decisions for their patients than for themselves.
d. make different decisions for themselves and their patients.
e. cannot decide for either one.

28. Hs-CRP may be useful in acute viral or idiopathic pericarditis for:

a. establishing the diagnosis.
b. determining the duration of therapy.
c. suggesting when to escalate therapy.
d. All of the above

Answers: 27. d, 28. d

CME Objectives

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

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda.

Vitamin D and Hypertension

Source: Bhandari SK, et al. 25-hydroxyvitamin D levels and hypertension rates. *J Clin Hypertens* 2011;13:170-177.

Let's make this simple: vitamin D deficiency causes EVERYTHING. Well, at least that's the way things seem these days. In addition to the widespread awareness that insufficient vitamin D — as demonstrated by measurement of serum 25-hydroxy-vitamin D — is rampant, maladies from all spheres of medicine are increasingly recognized to be associated, to one degree or another, with vitamin D. Today, it is hypertension.

Bhandari et al begin their discussion of the relationship between vitamin D and hypertension (HTN) by pointing out that as many as 40% of U.S. adults are vitamin D deficient. Epidemiologic analyses suggest that all-cause mortality is lower in vitamin D supplemented persons. Because vitamin D is involved with the renin-angiotensin-aldosterone system, it does not require a great stretch of the imagination to visualize a vitamin D-HTN linkage.

The data studied by the authors include 2,722 adult members of the Southern California Kaiser Permanente health care system. Rates of HTN were compared with quartiles of vitamin D. A linear and inverse relationship between vitamin D status and HTN was observed, such that individuals in the lowest vitamin D quartile were almost three times as likely to have HTN as those in the highest quartile.

Whether vitamin D supplementation could improve blood pressure or prevent development of HTN remains to be determined. In the meantime, add another item to the growing list of health issues in some way linked to vitamin D status. ■

Amitriptyline vs Duloxetine for Diabetic Peripheral Neuropathic Pain

Source: Kaur H, et al. A comparative evaluation of amitriptyline and duloxetine in painful diabetic neuropathy. *Diabetes Care* 2011;34:818-822.

Diabetic peripheral neuropathic pain (DPNP) is challenging because not only does it induce a substantial pain burden, but also the pain is typically worse at night — resulting in sleep deprivation — and exacerbated by activity, compromising the ability of patients to perform the exercise that is so critical in weight control. Although only two drugs have received specific FDA approval for management of DPNP (pregabalin, duloxetine), clinicians often use drugs off-label, including amitriptyline. Few head-to-head trials are available with which to compare various commonly used agents.

Kaur et al performed a double-blind crossover trial of amitriptyline (up to 50 mg/d) vs duloxetine (up to 60 mg/d) in 58 study subjects. The primary outcome was patient-assessed global efficacy at 6 weeks.

The outcomes with duloxetine and amitriptyline were essentially equivalent, and tolerability was also quite similar, although dry mouth was statistically significantly more common with amitriptyline. Comparable improvement in sleep was also seen with both medications. Since amitriptyline is available generically at a low price, it presents a viable therapeutic alternative for patients whose dry mouth is not a limiting adverse effect. ■

Testosterone Replacement in Diabetes and the Metabolic Syndrome

Source: Jones TH, et al. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES 2 Study). *Diabetes Care* 2011;34:828-837.

Both metabolic syndrome (MBS) and type 2 diabetes (DM2) have been consistently found to be associated with low testosterone (TST) levels. Several new formulations of topical TST have become available in the last few years, simplifying treatment of hypogonadism. Jones et al studied the effects of TST 2% gel daily applications in hypogonadal men with MBS or DM2 treated for 1 year.

TST replacement produced numerous favorable effects in these hypogonadal men, including improvements in insulin resistance, a reduction in A1c, and lower LDL and lipoprotein A. Decreased libido and reduced sexual function are the most common presenting symptoms of hypogonadism, and numerous clinical trials have confirmed a prompt, sustained favorable response in these domains, which was similarly confirmed in this trial.

Tolerability of TST 2% gel was similar to placebo. When adverse effects did occur, more than 96% were considered mild or moderate. Cardiovascular (CV) events were seen more often in the placebo group, a reassuring finding since another trial published recently found a disarmingly marked increase in CV events in frail, senior men treated with TST.

In addition to improving target symptoms for which hypogonadal men seek relief, TST replacement can provide several other favorable metabolic effects in persons with DM2 or MBS. ■

In Future Issues:

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