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Vitamin D Deficiency and Cardiovascular Health

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

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

Synopsis: *Vitamin D deficiency is associated with a significant risk of cardiovascular disease and reduced survival. Vitamin D supplementation improved survival, especially in patients with documented deficiency.*

Source: Vacek JL, et al. Vitamin D deficiency and supplementation and relation to cardiovascular health. *Am J Cardiol* 2012;109:359-363.

It is well known that cardiovascular disease is the most common cause of mortality and morbidity, accounting for nearly 30% of all deaths worldwide in 2003. In addition to its well-defined role in bone and calcium metabolism, vitamin D deficiency has been identified as an important factor in cardiovascular health. In fact, recent published reports have highlighted the presence of significant vitamin D deficiency in subjects with hypertension, peripheral vascular disease, diabetes mellitus, the metabolic syndrome, coronary artery disease, and heart failure. In a recently reported 20 hospital multicenter study, almost all patients entering with an acute myocardial infarction were found to have abnormally low vitamin D levels.[1]

Vacek and his associates examined the relationship between vitamin D deficiency, vitamin D supplementation, and patient outcomes in a large cohort. Vitamin D measurements were observed over a 5-year and 8-month period of time in 10,899 patients. The vitamin D deficiency observed in 7665 of these patients was associated with several cardiovascular-related illnesses, including hypertension, coronary artery disease, cardiomyopathy, and diabetes, and it was a strong independent predictor of all cause mortality. In addition, vitamin D supplementation was associated with a sig-

nificantly improved survival rate, particularly in those patients with a documented deficiency.[2]

■ COMMENTARY

This observational, retrospective study[2] using a cohort of patients followed by a cardiovascular practice in a large academic medical center demonstrated a clear association between vitamin D deficiency and many cardiovascular disease states, including hypertension,[3-5] coronary artery disease,[6-7] cardiomyopathy,[6] and multiple cardiovascular risk factors including hypertension, diabetes mellitus, and hyperlipidemia. Multiple prior studies have suggested that vitamin D deficiency was associated with poor patient outcomes[8-9] and, equally important, the Vacek study[2] is one of the first papers to demonstrate better survival with vitamin D supplementation. However, additional investigation with long-term prospective studies of various vitamin D dosage levels in both healthy and vitamin D-deficient populations are indicated to firmly establish the role of vitamin D supplementation on overall outcomes and mortality. Patient compliance, dose and duration of vitamin D supplementation, and outcomes will all have to be carefully analyzed in a well-designed prospective study in various patient populations. While waiting for the results of these important studies, clinicians should consider treating most, if not all, of their vitamin D-deficient patients with 1000-2000 IU of vitamin D daily until their vitamin D levels reach normal values. ■

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Questions & Comments
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How Often Should Healthy Women be Screened for Osteoporosis?

ABSTRACT & COMMENTARY

By Elizabeth Micks, MD, and Alison Edelman, MD, MPH

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This article originally appeared in the April issue of OB/GYN Clinical Alert. *At that time it was peer reviewed by Catherine Leclair, MD, Associate Professor, Department of OB/GYN, Oregon Health & Science University, Portland, OR. Drs. Leclair, Micks, and Edelman report no financial relationships relevant to this field of study.*

Synopsis: *In a prospective study of nearly 5000 postmenopausal women, it was determined that it would take 16.8 years to develop osteoporosis in 10% of women with normal bone mineral density. The authors conclude that repeat screening in women without new risk factors can be delayed for at least 15 years.*

Source: Gourlay ML, et al. Bone-density testing interval and transition to osteoporosis in older women. *N Engl J Med* 2012;366:225-233.

In this study, 4957 women aged 67 and older were followed prospectively for up to 15 years. Statistical models were used to calculate the bone mineral density (BMD) testing interval for women with normal BMD and those with mild, moderate, or advanced osteopenia. The BMD testing interval was defined as the number of years it would take for 10% of women to develop osteoporosis, before having a hip or vertebral fracture and before any treatment for osteoporosis was initiated. For women with normal BMD, the BMD testing interval was determined to be 16.8 years (95% confidence interval [CI] 11.5-24.6). For women with mild osteopenia (T score -1.01 to -1.49), the interval was 17.3 years (95% CI 13.9-21.5). More frequent testing intervals were found for those with moderate (T score -1.5 to -1.99, 4.7 years, 95% CI 4.2-5.2) and advanced (T score -2.0 to -2.49, 1.1 years, 95% CI 1.0-1.3) osteopenia.

■ COMMENTARY

Osteoporosis, diagnosed by low BMD on dual-energy x-ray absorptiometry (DEXA) scan, is well known to cause significant morbidity and mortality in postmenopausal women.[1] BMD accounts for at least three-fourths of the variation in bone strength, and is by far the strongest predictor of fracture risk.[2] The American Congress of Obstetricians and Gynecologists (ACOG) and other organizations recommend that all women have DEXA scans starting at age 65, or sooner if they have risk factors for osteoporosis.[3] In terms of subsequent screening, however, there has been little evidence for when to recommend the next DEXA scan. The U.S. Preventive Services Task Force[4] and ACOG[3] currently recommend only that the screening interval should be no more than every 2 years. This important new study provides data on the optimal screening intervals for women with normal BMD, and those with varying degrees of osteopenia.[5]

To review, The World Health Organization (WHO) uses the T score in its widely used definitions of osteoporosis and osteopenia.[6] Osteopenia is diagnosed if hip T score is between -1 and -2.5, meaning between 1 and 2.5 standard deviations below the mean peak BMD in a young adult population. A patient with a T score of ≤ -2.5 has osteoporosis. The main outcome for this particular study was "BMD screening interval," defined as the amount of time it would take for 10% of women to develop osteoporosis after a baseline screening test. The study is not a cost-benefit analysis of DEXA screening for osteoporosis, and the authors don't provide any clear justification for this definition.

The BMD screening interval was found to be 16.8 years for those with normal BMD, and 17.3 years for those with mild osteopenia. Surprisingly, less than 1% of women with normal BMD (T score > -1.00) and 5% of women with mild osteopenia (T score -1.01 to -1.49) actually developed osteoporosis during the 15-year study period. The study found 2.4% of subjects had a hip or vertebral fracture before osteoporosis was diagnosed. Even without critiquing the statistics used by the study authors, we can reassure our patients with normal BMD or mild osteopenia that it is safe to delay repeat screening for much longer than previously thought.

The data were not as reassuring for those with moderate (T score -1.50 to -1.99) or advanced osteopenia (T score -2.00 to -2.49). About 20% of women with moderate osteopenia, and more than 62% of those with advanced osteopenia, developed osteoporosis during the study period. The BMD testing interval for moderate os-

Clinical Tips

- Osteoporosis screening should be initiated at age 65 in healthy women with no risk factors for osteoporosis.
- Younger women should undergo screening if their fracture risk is equivalent to that of a 65-year-old woman.
  - Risk factors include family history of osteoporosis, Caucasian race, smoking, early menopause (less than 45 years), and certain medications. See ACOG Practice Bulletin No. 50: Osteoporosis for a complete list of medical conditions, medications, and other factors that increase a woman's fracture risk: (www.acog.org/Resources_And_Publications/Practice_Bulletins)
  - Use the FRAX Fracture Risk Assessment Tool to calculate a patient's 10-year fracture risk and timeframe for screening (www.shef.ac.uk/FRAX/).
- Osteoporosis develops slowly in women with normal bone density or mild osteopenia.
  - For women with normal BMD and no new risk factors, repeat screening can likely be safely delayed for 15 years.
- Women with moderate or severe osteopenia warrant more frequent screening.

teopenia was found to be 4.7 years, and just 1.1 years for advanced osteopenia.

Analysis also was performed stratifying by significant clinical risk factors including age, BMI, and baseline estrogen use. Within a specific T-score group, younger women were found to have a longer time interval to osteoporosis. For women with osteopenia, estrogen use during the baseline exam was associated with a longer time interval to osteoporosis. Unfortunately, this did not apply to women who reported prior estrogen use, indicating that the positive effect of estrogen on BMD is not long lasting. For women with advanced osteopenia, higher BMI was associated with a longer time interval to osteoporosis. Other risk factors — including smoking, glucocorticoid use, rheumatoid arthritis, and any fracture after age 50 — were not significant predictors of osteoporosis in this study, even among women with osteopenia at baseline.

When actual fracture risk rather than osteoporosis was examined as the outcome, it was determined that it would take more than 15 years for 2% of women with normal BMD or mild osteopenia to have a femoral or clinical vertebral fracture.

An earlier analysis of the Study of Osteoporotic Fractures (SOF), the same study population as the current publication, in 2007 showed that repeat BMD screening at up to 8 years did not contribute to better prediction of fracture risk beyond the baseline screening.[7] To date, these are the only longitudinal studies addressing the optimal frequency of DEXA scans.

For the SOF, 9704 women aged 65 or older in four sites within the United States participated in at least one study examination. From this initial group, 8497 women had adequate baseline BMD data. Of these, about 25% were excluded because they were found to have osteoporosis, and 200 were excluded because they already had a femoral or vertebral fracture or had taken calcitonin. An additional thousand subjects were excluded because they were lacking follow-up data. A total of 4957 subjects were included in the present analysis. Subjects underwent study examinations at year 2, year 6, year 8, year 10, and year 16. Based on T scores, cumulative incidence curves for the time to osteoporosis were developed.

This large prospective, longitudinal study provides much needed evidence for the optimal interval between DEXA scans in women with normal BMD or osteopenia. While we await revised guidelines from ACOG and the U.S. Preventive Services Task Force, we can counsel our patients that osteoporosis develops slowly. ■

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Myocardial Infarction Symptom Presentation

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

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This article originally appeared in the April 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. Dr. Boyle reports no financial relationships relevant to this field of study.*

Synopsis: *The authors conclude that in patients hospitalized with myocardial infarction, women were more likely than men to present without chest pain and had higher mortality than men within the same age group.*

Source: Canto JG, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA* 2012;307:813-822.

Timely recognition and treatment of myocardial infarction (MI) are crucial if we are to achieve optimal outcomes for our patients. Silent ischemia, or the absence of classical symptoms of ischemia, may delay the diagnosis. In patients presenting with MI, delay in diagnosis and treatment may have disastrous outcomes. Accordingly, Canto and colleagues analyzed data from the National Registry of MI (NRMI) to assess the frequency

with which men and women were admitted for MI without chest pain and the effect that presenting without chest pain has on mortality.

The investigators studied more than 1.1 million patients (42% women) presenting with MI, both ST elevation MI (STEMI) and non-ST elevation MI (non-STEMI) from 1994-2006. The in-hospital mortality rate was 14.6% for women and 10.3% for men ($P < 0.001$). The proportion of MI patients who presented without chest pain was an alarming 35%. Women presenting with MI were more likely than men to present without chest pain (42% vs 31%; $P < 0.001$). In addition, advancing age was associated with higher rates of MI without chest pain, but interestingly the gender differences actually became less pronounced with age. Patients presenting without chest pain were more likely to have diabetes, to have delayed presentation, to present with non-STEMI, and to present in Killip class III or IV, whereas those with chest pain were more likely to present with anterior MI and STEMI. Patients without chest pain were less likely to receive aspirin, beta-blockers, antithrombins, antiplatelet agents, or reperfusion therapy. Furthermore, when they did receive the appropriate treatments, those who presented without chest pain experienced significant delays.

After statistical adjustment for clinical characteristics, comorbidities, treatments received, and delays, younger men and women who suffer MI without chest pain were more than twice as likely to die from their MI than those who had chest pain. However, with advancing age this difference was attenuated, and at age ≥ 75 years men were 32% more likely to die and women were 8% more likely to die than their counterparts with chest pain. The authors conclude that in patients hospitalized with MI, women were more likely than men to present without chest pain and had higher mortality than men within the same age group, but sex differences in clinical presentation without chest pain and in mortality were attenuated with increasing age.

■ COMMENTARY

I am struck by the significant rate of MI without chest pain (35%) in this study. Although this was higher in women (42% vs 31%), the rate of MI without chest pain is still alarmingly high in both sexes and we should have a high index of suspicion for acute MI in patients with atypical presentations. One may intuitively think that non-STEMI were more likely to present without chest pain than STEMI. This is true in the current study, but interestingly more than one-third of all STEMI also presented without chest pain. Delays in treatment were seen in patients without chest pain, and this could lead to serious outcomes in MI patients. This was demonstrated by the higher mortality in those without chest pain in this study. Interestingly, the difference between genders became less apparent with age, but the total proportion of patients presenting with MI without chest pain increased. The reasons for this remain unknown.

The major limitation of this study is that it is a retrospective analysis of registry data. The participating hospitals may not have collected data equally, and the hospitals participating in the NRMI registry may not serve populations that are truly representative of all regions throughout the United States. However, this is an incredibly large study — involving more than a million patients — which strengthens the conclusions made. We should continue to be vigilant for atypical presentations of MI, particularly in women and older patients. Hopefully, increased awareness of painless MI presentation may hasten diagnosis and avoid treatment delays for our patients. ■

Is a Family History of Cardiovascular Disease Valuable?

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Professor of Medicine, University of California, San Francisco, Chief of Clinical Cardiology, University of California, San Francisco Medical Center

This article originally appeared in the April 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. Dr. Crawford reports no financial relationships relevant to this field of study.*

Synopsis: *The authors concluded that systematically obtaining family history identifies more subjects with high CV risk who may benefit from more aggressive preventive interventions.*

Source: Qureshi N, et al. Effect of adding systematic family history inquiry to cardiovascular disease risk assessment in primary care: A matched-pair, cluster randomized trial. *Ann Intern Med* 2012;156:253-262.

ALTHOUGH A ROUTINE PART OF A COMPLETE MEDIcal history, the value of systematically collecting family history has not been shown in controlled trials. Thus, these investigators from the United Kingdom sought to determine the feasibility of collecting a detailed family history and whether this information would identify more high-risk individuals for cardiovascular (CV) disease. Matched Family Practice pairs were randomly assigned to the family history interven-

tion or usual care. Both groups received standard CV risk assessment. The intervention group family history was collected by a self-administered questionnaire. The primary outcome measure was the number of subjects classified as high risk for CV disease based on the two approaches (10-year risk > 20%). Also, anxiety levels were assessed by a standard questionnaire.

A total of 748 subjects from 24 family practices with no history of CV disease participated. The family history questionnaire was completed by 98% of the subjects. The increase in high-risk patients was 41% in the questionnaire group vs 6% in the usual care group where family history was obtained from the medical records. Anxiety levels were not increased by this intervention. The authors concluded that systematically obtaining family history identifies more subjects with high CV risk who may benefit from more aggressive preventive interventions.

■ COMMENTARY

This study objectively confirms the value of family history in CV disease prevention. A preliminary survey by the investigators demonstrated that often family history was not recorded in the medical record. One reason for this is the limited time available during the health visit. This was overcome in the intervention group by having the subjects fill out a questionnaire before the visit, which was feasible 98% of the time in this study population. The risk profile of the control group was obtained from the Framingham score, which does not incorporate family history but is widely used in the United Kingdom and the United States.

One of the strengths of the study was the pairing of practices involved with the same patient population, which eliminates ethnic or cultural differences in the groups that were compared. However, a weakness of the study is that few ethnic minorities or low education level subjects were included. Also, there were not a lot of smokers in the subjects studied. However, among the usual care group no one quit smoking, but 6 (20%) smoked less at 6 months of follow-up. Among the intervention group, 10 quit and 8 reduced their smoking (62%). Aspirin use increased among the intervention group as compared to the control group (48 vs 31% increase), but increases in statin use were the same. The patients reclassified as high risk in the intervention group were in the moderate-risk group before (Framingham risk 10-20% over 10 years). In the United Kingdom, aspirin use is not recommended for such patients. Unfortunately, there are no outcome data in this study. Clearly, employing a more robust analysis of family history is feasible in some primary care practices, but whether this influences therapy and prevents CV events remains to be proven. ■

Pharmacology Update

Avanafil Tablets (Stendra™)

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 relationships relevant to this field of study.

A NEW SELECTIVE PHOSPHODIESTERASE TYPE 5 (PDE5) INHIBitor has been approved for treating erectile dysfunction (ED). Avanafil was developed by Mitsubishi Tanabe Pharma Corporation in Japan and is manufactured in Japan and marketed by Vivus, Inc., as Stendra.

Indication

Avanafil is indicated for the treatment of ED.[1]

Dosage

The recommended dose is 100 mg taken without regard to a meal about 30 minutes before sexual activity.[1] The dose may be increased to 200 mg or reduced to 50 mg based on effectiveness or adverse events. When taken with a moderate CYP3A4 inhibitor, the dose should not exceed 50 mg. Avanafil should not be taken more than once in 24 hours.

Avanafil is available as 50 mg, 100 mg, and 200 mg tablets.

Potential Advantages

Avanafil is highly selective for PDE5, compared to sildenafil, and has a rapid onset of action.

Potential Disadvantages

The most frequently reported adverse events were headache, flushing, nasal congestion, nasopharyngitis, and back pain.[1] Frequencies range from 1% to 10%. Avanafil is contraindicated in patients taking strong CYP 3A4 inhibitors or CYP inducers. Avanafil carries the same class contraindications and precautions as other PDE5 inhibitors, including the risk of sudden vision change or loss and sudden hearing loss.

Comments

Avanafil has a rapid onset of action with mean time

to peak concentration of approximately 0.6 hours. This compares to approximately 1 hour for sildenafil 100 mg, 2 hours for tadalafil 20 mg, and is similar to 0.66 hours for vardenafil 20 mg.[2] Its elimination half is approximately 1 hour — the shortest of these agents. This compares to 4 hours for sildenafil and more than 17 hours for tadalafil. It also has high selectivity for PDE5 compared to PDE6 compared to sildenafil and vardenafil.[2] Inhibition of PDE6 has been implicated in visual symptoms.[3] The efficacy and safety of avanafil was evaluated in two Phase 3, placebo-controlled, 12-week clinical trials.[1] Study 1 (TA-301) randomized subjects (n = 646) with ED to placebo, avanafil 50 mg, 100 mg, or 200 mg. The primary endpoints were improvement in the International Index of Erectile Function (IIEF) and Sexual Encounter Profile questionnaires (SEP2 and SEP3). SEP2 assesses successful vaginal penetration and SEP3 assesses the ability to successfully complete intercourse. Statistically significant IIEF improvements were seen with all three doses of avanafil compared to placebo. From a baseline of 12.4 to 12.7, avanafil increased the IIEF score by 5.4, 8.3, and 9.5 points for the three doses compared to 2.9 for placebo. From a baseline of 45% to 48%, avanafil showed an absolute mean increase in SEP2 by 18%, 27%, and 30%, respectively, compared to 7% for placebo. SEP3 (baseline 12-14%) improved by 28%, 43%, and 44% compared to 14%, respectively. Two-thirds to almost three-fourths of the men who attempted sexual intercourse within 15 minutes were successful.[2] In study 2 (TA-302), diabetics with erectile dysfunction (n = 302) were randomized to placebo or avanafil 100 mg or 200 mg. The results were similar although there was a lower magnitude of improvement in IIEF and SEP3.[1] Avanafil is being evaluated in patients with post-radical prostatectomy.

Clinical Implications

Avanafil is the newest PDE5 inhibitor approved for the treatment of ED. It is characterized by rapid onset and short duration of action, but no clear clinical advantages in terms of effectiveness or safety have been demonstrated. ■

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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.

CME Questions

1. Vitamin D deficiency:
   a. rarely occurs under the age of 40 or in African Americans.
   b. is not a significant risk factor for cardiovascular disease.
   c. has not been observed to occur with increased frequency in patients with acute myocardial infarctions.
   d. is definitely associated with a significant risk of cardiovascular disease and reduced survival.

2. According to current ACOG guidelines, how often should women with normal bone mineral density (BMD) and no new risk factors for osteoporosis undergo BMD screening?
   a. Every 10 years
   b. Every 5 years
   c. Not more frequently than every 2 years
   d. Not more frequently than every year

3. All of the following are risk factors for osteoporotic fractures in postmenopausal women, *except*:
   a. obesity.
   b. alcoholism.
   c. smoking.
   d. family history of osteoporosis.

4. The occurrence of acute myocardial infarction without chest pain is about:
   a. 5%.
   b. 10%.
   c. 25%.
   d. 35%.
   e. None of the above

5. A systematically taken family history of cardiovascular disease can:
   a. improve the identification of high-risk individuals.
   b. increase patient anxiety.
   c. not be successfully accomplished in busy practices.
   d. not impact smoking behavior.
   e. All of the above

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

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

Cancer Risks Associated with Diagnostic X-rays

Source: Linet MS, et al. *CA Cancer J Clin* 2012;62:75-100.

Within a few years after the initiation of diagnostic X-rays, toxic effects were noted, including increased risk for skin cancer, leukemia, dermatitis, and cataracts. In this early period, doses of X-ray, especially from fluoroscopy, were high. Protective devices for patients as well as persons occupationally exposed to diagnostic radiation demonstrably reduced such adverse consequences.

The dose of radiation that is required to induce cancer is not clearly known. However, populations who have been exposed to calculable levels of radiation through wartime exposure (i.e., Japanese atomic bomb survivors) and subjects receiving radiation therapy help us to predict a dose-response relationship. It is not yet clear to what extent the high-dose radiation exposure and subsequent development of cancer reflects cumulative lower dose exposures. Nonetheless, because radiation toxicity may be related to total exposure, peak exposure, or both, radiation from commonly used diagnostic procedures has stimulated concern.

For instance, a CT of the abdomen, commonly used investigationally for persons with acute or chronic abdominal pain, incurs the same amount of radiation exposure as 750 chest X-rays. Linet et al quote recent estimates suggesting that the 70 million CT scans performed each year in the United States could lead to 29,000 additional cancers.

The authors recommend a number of steps to reduce unnecessary radiation exposure, including 1) learning about radiation doses associated with various imaging techniques, 2) consideration of imaging without radiation (i.e., ultrasound, MRI), and 3) avoidance of elective X-rays in pregnant women. ■

The REDEEM Trial: Dutasteride for Management of Localized Prostate Cancer

Source: Fleshner NE, et al. *Lancet* 2012; 379:1103-1111.

Prostate cancer (PCA) comprises 25% of all newly diagnosed cancers in men in the United States. PCA chemoprevention trials with 5-alpha-reductase inhibitors have had mixed results. The first major PCA prevention trial with finasteride showed a 25% decrease in total PCA vs placebo, but an increase in more aggressive (high Gleason score) cancers. A similarly designed large prevention trial with dutasteride again found a 25% decrease in total PCA, but there was an increase in more aggressive cancers (albeit not statistically significant in this trial). Based on these mixed results, clinicians have been reluctant to use 5-alpha-reductase inhibition for PCA prevention.

Might 5-alpha-reductase inhibitors prove more useful for treatment of PCA rather than prevention? The REDEEM trial randomized men with localized PCA (n = 300) who had elected active surveillance for their disease to dutasteride 0.5 mg/d or placebo. At 3 years time, the risk of PCA progression was reduced by 38% in men on dutasteride.

Because dutasteride is generally well tolerated, men with non-aggressive Gleason scores (six or less) who might otherwise select active surveillance for localized disease may have reduced risk of disease progression with the addition of dutasteride. ■

Amantadine for Traumatic Brain Injury

Source: Giacino JT, et al. *N Engl J Med* 2012;366:819-826.

In young adults (age 15-30), traumatic brain injury (TBI) is the most common cause of death and disability. As many as one in seven TBI hospital admissions leaves the hospital in a vegetative state. Amantadine (AMT) has achieved some popularity for inclusion in pharmacotherapy regimens for disorders of consciousness, although the mechanism by which AMT effects positive change is uncertain. Certainly it has been shown that AMT blocks N-methyl-D-aspartate, and is an indirect agonist of dopamine, but what these pharmacologic effects do to enhance outcomes is unclear. In any case, initial trials have supported its use, and a major observational trial indicated better outcomes in TBI for persons who had received AMT.

Patients who had sustained TBI (n = 184) and who were either vegetative or minimally conscious for at least 1 month (and no longer than 16 weeks) after injury were randomized to AMT or placebo. AMT was administered initially at 100 mg b.i.d., and titrated to 200 mg b.i.d. if the Disability Rating Scale had not shown improvement. The course of treatment was 4 weeks in duration, and patients were monitored for 2 weeks after discontinuation of treatment.

AMT treatment was associated with statistically significantly better functional recovery outcomes than placebo. AMT is not a new medication, so its adverse effects profile, characterized by mild, transient adversities, is well known. These data support the inclusion of AMT in the pharmacologic regimen of serious TBI. ■

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