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INSIDE

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Lower Testosterone Linked to Increased Fracture Risk in Men

ABSTRACT & COMMENTARY

By Mary Elina Ferris, MD

Clinical Associate Professor, University of Southern California

Dr. Ferris reports no financial relationship with this field of study.

Synopsis: *Lower serum testosterone in men aged 60 and over was associated with increased fracture risk (especially hip and nonvertebral), even after adjusting for other major risk factors for fracture.*

Source: Meier C, et al. Endogenous sex hormones and incident fracture risk in older men: the Dubbo Osteoporosis Epidemiology Study. *Arch Intern Med.* 2008;168:47-54.

An ongoing osteoporosis study in the Australian town of Dubbo is following men and women (predominately Caucasian) aged 60 and over, with baseline bone mineral density (BMD), serum samples for sex hormone-binding globulin (SBHG), estradiol (E2) and testosterone, and for fracture incidence at 2-year intervals. After almost 6 years, the authors report on a sample of 609 men, 113 of whom were found to have a total of 149 fracture incidents, or 3.4 per 100 person-years. Men with fractures were older, had lower body weight, and lower dietary calcium. Nearly 80% of the fractures occurred in men aged 70 years and older, which was 2.7-fold higher than those under age 70.

For all men, both serum testosterone and E2 decreased with age and weight, with the reverse for SHBG, which showed higher levels with age. Increased risk of fractures was significantly associated with low levels of serum testosterone but not with E2 levels, which were similar in both the fracture and non-fracture groups. Although serum E2 was positively related to BMD, there was no significant relationship between testosterone and BMD. The effect of lower testosterone on increased fracture risk in non-vertebral sites persisted independent of other risk factors including age, low BMD, smoking, prior fracture or low calcium intake. Analysis adjusting for multiple other variables, including SHBG, showed that each standard deviation decrease of serum testosterone gave an increased fracture risk of 30-40%.

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COMMENTARY

Increasing evidence points to the vital role that sex steroids play in the maintenance of bone health, and more attention is being focused on osteoporosis in men. It's now thought that fully one-third of osteoporotic fractures occur in men, making the lifetime risk for hip and vertebral fractures in men similar to that of prostate cancer.

Studies in the past gave conflicting results about the role of serum testosterone, such as the Framingham study, which linked low estradiol and testosterone levels together, but not alone, with increased fractures in men.[1] Swedish studies have positively linked free testosterone with fractures,[2] while a smaller Rotterdam study did not.[3] However, measurement of testosterone in the past used immunoassay-based methods which are not as reliable for low levels as the current liquid chromatography tandem mass spectrometry method. Furthermore, bioavailable or "free" testosterone is dependent on how much of it is bound to sex hormone-binding globulin (SBHG). Previous values for free testosterone were often calculated using this measurement, which has its own limitations.

While the explanation for testosterone's influence on bone health is not yet understood, we do know that peak bone mass in young men is associated with higher testosterone and lower estrogens,[4] which is thought to account for gender-specific differences in bone mass. It seems plausible that a decrease in testosterone with ageing would also have a role in bone health. This study suggests that serum testosterone levels are an independent risk factor for fractures, and this is a separate risk from low BMD. However, these results do not establish a causal relationship, and the study does not address whether testosterone replacement would alter fracture risk in older men. ■

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My Achin' Back!

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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

Synopsis. *Neither training in working techniques nor use of lifting equipment appears to prevent back pain or back-related disability.*

Source: Kari-Pekka Martimo K, et al. Effect of training and lifting equipment for preventing back pain in lifting and handling: systematic review. *BMJ.* 2008. (doi:10.1136/bmj.39463.418380.BE)

THIS REPORT IS THE RESULT OF A META ANALYSIS that was conducted using detailed searching of multiple databases to find studies that aimed to modify the

participants' lifting techniques at work and which measured back pain, consequent disability, or absence related to back pain as the main outcomes. The authors found 11 out of 3611 possible studies that were of high enough quality and detail to be included in this meta analysis. Of these, 6 were randomized trials and 5 were cohort studies. Most of the studies (three randomized trials and five cohort studies) involved care of patients. One trial studied postal workers and two investigated baggage handlers. The number of participants in these reports varied from 45 to 12,772, and the follow-up times ranged from eight weeks to 5.5 years. The authors included only analyses of workers who were not actively seeking treatment for current back pain at the time of enrollment, and who had enough work-related strain on the back so that intervention might reasonably be expected to make a difference. The training interventions that were assessed in the included trials were generally the use of instruction on lifting techniques varying in intensity from a single session to training once a week for two years. In some reports, the training was supported by follow-up and feedback in the workplace. Five of the included studies encouraged participants to use available lifting aids, and some used a professional instructor.

There was no difference in back pain (odds ratio 0.99, 95% confidence interval 0.54 to 1.81) or related disability at intermediate or long-term follow-up when comparing the groups that received training to those who received no intervention in the randomized trials. Similar findings were demonstrated in the cohort studies. With regard to use of lifting equipment, a comparison of a group receiving training and lifting equipment with the groups receiving training only or no intervention at all in one randomized trial showed no difference in back pain or back-related disability at intermediate follow-up of either comparison.

The authors note, "Many health professionals are involved in training and advising workers on lifting and handling. Even though there may be other reasons to continue this practice, this review does not provide evidence that it prevents back pain."

COMMENTARY

Revolutionary as it seems, this paper is not the only evidence that we are wasting a lot of time and energy on useless training with regard to prevention of back problems. Apparently too late to be included in this analysis, two other relevant, high quality trials have recently been published. One of these showed no effect of training in transfer techniques on subsequent back pain on a two year follow-up of health care workers caring for elderly people.[1] The other failed to show that training on lifting in a distribution center affected rates of back injury over a one year follow-up.[2]

Specific techniques to reduce the load on the back have been advocated by highly respected authorities;[3,4] we appear to have developed an entire, unsubstantiated dogma about how to prevent back injury; At present, there does not seem to be much evidence to support the use of these (or any other) training techniques to prevent back injury related to heavy lifting. Yet back pain and its prevention are big business because back pain is highly prevalent and enormously expensive, particularly among workers lifting heavy loads. The answers are most definitely not in yet. For now, the best strategy would appear to be avoiding heavy loads altogether!

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Disruptive Behavior in Alzheimer's Disease

ABSTRACT & COMMENTARY

By Michael Lin, MD

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

This Abstract was originally published in the March 2008 issue of Neurology Alert.

Synopsis: *Disruptive behaviors are a poor prognostic sign in patients with Alzheimer's disease.*

Source: Scarmeas N, et al. Disruptive behavior as a predictor in Alzheimer disease. *Arch Neurol* 2007;64:1755-1761.

Disruptive behavioral symptoms (DBSs) such as wandering, outbursts, threats/violence, agitation/restlessness, and sundowning are well known to occur in Alzheimer's disease (AD), particularly as the disease

advances. Somewhat surprising, however, is that the relationship between DBSs and disease outcomes has not been consistent in the literature, possibly due to variability in symptom ascertainment, disease stage, and consideration of neuroleptics.

To address the relationship between DBSs and disease outcomes in AD, Scarmeas and colleagues analyzed 497 patients with moderate AD (average MMSE [Mini Mental State Examination] 20.4, range 5-30), recruited from 5 university-based memory disorders clinics in North America and Europe. Subjects were examined every 6 months for an average of 4.4 years, and the presence of DBSs was assessed using the Columbia University Scale for Psychopathology in AD. Use of cholinesterase inhibitors and neuroleptics was also recorded.

The primary endpoints of the study were: 1) cognitive outcome (Folstein MMSE $\leq$ 10/30); 2) functional outcome (Blessed Dementia Rating Scale Parts I and II score $\geq$ 10/17); 3) institutionalization (as determined by actual institutionalization or an equivalent institutional care dependency scale); and 4) mortality.

DBSs were extremely common. Although only 48% of subjects exhibited a DBS at baseline, this rose to 83% at some point during follow-up. Throughout followup, subjects had on average 2.3 +/- 1.5 DBSs, which increased over time. Agitation/restlessness was present in ~3 of every 4 patients, outbursts and sundowning in ~1 of every 2 patients, and wandering and threats/violence in ~1 of every 3 patients.

DBSs also were predictive of disease outcomes, increasing the risks of cognitive decline, functional decline, and institutionalization each by a factor of approximately 1.5. There was no effect on mortality. Specific DBSs appeared to be more strongly predictive of certain outcomes than others. Neuroleptic use was associated with a higher risk of functional decline (hazard ratio [HR] 1.57) and institutionalization (HR 1.57), but not with cognitive outcome or mortality. Cholinesterase inhibitors were associated with a lower risk of institutionalization (HR 0.47) and mortality (HR 0.36), but not with cognitive or functional outcomes.

Finally, autopsy data were available for 96 patients. Ninety-three percent of cases had AD-type pathology, 21% of which also had Lewy body pathology. Exclusion of subjects with Lewy body pathology did not change the prevalence of DBSs or their association with the disease outcomes.

This is a strong study, one of the largest to examine DBSs in AD. It was conducted at university centers by experts in memory disorders, had extensive and nearly complete follow-up (94%), and assessed all the variables of interest over multiple visits in a time-dependent fashion. On the other hand, the population was limited to highly specialized referral centers and was predominantly Caucasian with few comorbidities; this potentially limited the ability to generalize the results. Assessment of predictors and outcomes was conducted by the same examiners, a potential source of bias. The neuropathology underlying DBSs and their association with disease outcomes remain to be explored.

The take home points of this article include the very high prevalence of DBSs in AD, and their predictive value for disease outcomes. Additionally, the study provides further evidence for use of cholinesterase inhibitors in improving disease outcome, and for minimizing the use of neuroleptics. ■

Effects of Eliminating Daily Chest X-Rays in the ICU

ABSTRACT & COMMENTARY

By Saadia R. Akhtar, MD, MSc

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

This abstract originally appeared in the March 2008 issue of Critical Care Alert.

Synopsis: *This single center prospective observational study finds that the utility of a routine daily chest x-ray (CXR) for an ICU patient is quite limited. A change in practice to ordering CXR only when clinically indicated did not adversely impact patient outcome but reduced CXR volume and overall costs.*

Source: Hendrikse KA, et al. Low Value of Routine Chest Radiographs in a Mixed Medical-Surgical ICU. *Chest.* 2007;132: 823-828.

A PROSPECTIVE OBSERVATIONAL STUDY WAS CONducted to assess diagnostic and therapeutic efficacies of a daily routine CXR and to evaluate the impact of discontinuing this practice. The setting was a 10-bed mixed medical-surgical ICU of a non-academic teaching hospital in The Netherlands. A daily CXR was obtained on every ICU patient every day for 1 year. These CXRs were read independently by

radiologists; images and reports were not available to the patient's attending physicians unless there was a new potentially life-threatening finding (eg, tension pneumothorax).

If the attending physician requested a CXR for a specific clinical indication close to the time the daily study CXR was obtained, this CXR was released for view; if the clinical indication arose at a different time, a new CXR was performed and made available to the physician. The authors documented data on specific new or progressive radiological findings (eg, malpositioning of hardware, infiltrates, pneumothorax, etc) and patient management decisions (adjustment of hardware, change in medications or ventilator settings, etc.) that were defined *a priori*. Finally, after a 1-year study period, routine daily CXRs were discontinued and both clinician practice and outcomes were observed for another 6 months. Cost estimates were determined a priori for each CXR, and standard statistical methods were employed.

There were 559 admissions in 486 patients during the 1-year study period, accounting for a total of 1780 daily routine CXRs; 907 additional clinically indicated CXRs were performed. Only 4.4% (79) of the daily routine CXRs, vs 15.2% (138) of the clinically indicated CXRs, revealed new or progressive radiological findings. This was independent of intubation status or admission type (medical vs surgical). Similarly, only 1.9% (33) of the daily routine CXRs, but 17.9% (162) of the clinically indicated CXRs, led to a change in patient management.

During the follow-up 6 month phase, 433 clinically indicated CXRs were performed during 274 admissions for 250 patients. That is, the total number of CXRs per patient per day decreased by about 50%. There was an associated cost reduction of $99,000 per year. There was no change in ICU length of stay, readmission rate, or hospital mortality noted, although the study was not designed or powered to truly detect differences in cost, ICU length of stay, readmission or mortality.

COMMENTARY

The ordering of a routine daily CXR for every ICU patient remains a common practice, despite prior work suggesting this may not be necessary.[1,2] The authors of the present article reasoned that because previous studies had been somewhat limited in terms of size, setting (most had been conducted at academic centers) or lack of blinding of attending physicians to the findings of daily CXRs, further research was indicated. Their prospective observational study is large, set in a non-academic center, and does blind attending physicians to the findings on daily CXRs. The latter is the greatest strength of this work: it allows the authors to demonstrate more clearly and robustly that clinical course and management are not often altered by knowledge of results of daily routine CXRs.

As might have been expected, the findings on clinically-indicated CXRs were much more likely to impact the course of care. Furthermore, between the 1-year study period and the 6-month follow-up phase, the number of clinically-indicated CXRs requested did not change, suggesting that the attending physicians' medical practice, standards and decision-making process were largely unaffected by the presence or absence of daily routine CXRs.

The authors address the limitations of their work thoroughly. The ideal would be a similar study but one conducted at multiple centers with a randomized, controlled design and powered to detect differences in clinical outcomes (length of stay, readmission, specific morbidities such as complications of a missed pneumothorax or delay in treatment of pneumonia, and mortality). However, taken together with the current body of literature on the limited utility or lack of utility of routine daily CXRs, Hendrikse et al's work reinforces the need to break this old habit.

A recently released study of accepted indications for CXRs in ICU patients surveyed 82 French intensivists and found that over 50% of them did not feel a daily routine CXR was needed in an intubated patient.[3] I wonder what a similar survey in the U.S. would reveal about our beliefs and our practice.

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Pharmacology Update

Desvenlafaxine Succinate Extended-Release Tablets (Pristiq™)

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

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

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

WYETH PHARMACEUTICALS HAS RECEIVED approval TO market desvenlafaxine for the treatment of depression. The drug is the major active metabolite of venlafaxine (Effexor). Wyeth has formulated the drug in a once-daily extended-release tablet. It will be marketed under the trade name Pristiq.

Indications

Desvenlafaxine is indicated for the treatment of major depressive disorder (MDD).[1]

Dosage

The initial dose is 50 mg once daily. Additional clinical benefit may not be gained with doses higher than 50 mg. For patients with severe renal impairment the recommended dose is 50 mg every other day. It may be taken without regard to meals. The tablets should be taken whole, not chewed, crushed, or divided. The tablet should be taken at the same time daily.[1]

Desvenlafaxine is available as 50 mg and 100 mg tablets.

Potential Advantages

Desvenlafaxine may provide a more consistent delivery of the major active component of venlafaxine with potentially less intrasubject and interpatient variability.[2] It also has a low potential for drug-drug interaction. Desvenlafaxine is metabolized from venlafaxine via CYP3A4.

Potential Disadvantages

Desvenlafaxine may increase blood pressure. It should not be started in patients with uncontrolled hypertension. Monitoring of blood pressure is recommended during treatment.[1] Nausea is the most common adverse event, ranges from 22% to 41%, and occurred during the first week of therapy.[3] It became less frequent by week 2. However, it was the leading cause for discontinuation of therapy.

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

Comments

Desvenlafaxine (O-desmethylvenlafaxine) is the major active metabolite of venlafaxine. It's similar to venlafaxine in its ability to inhibit the reuptake of serotonin and norepinephrine. Its efficacy in major depressive disorder was shown in four 8-week randomized, double-blind, placebo-controlled, fixed-dose studies.[1,3,4,5] These ranged from 50 mg to 400 mg daily. The primary endpoint was improvement in the 17-item Hamilton Rating Scale for Depression (HAM-D). In three studies, improvement in the Clinical Global Impression Scale (CGI-S) was used as a secondary endpoint also. In two published studies the results were mixed. One study some no difference between desvenlafaxine and placebo and the second showed significant difference for the 100 mg and 400 mg but not the 200 mg dose.[3,4] While desvenlafaxine has been studied with doses up to 400 mg daily, doses larger than 50 mg may not gain additional clinical benefit but is associated increase frequency of adverse events at higher doses.[1]

There is currently no evidence to suggest any significant difference in efficacy or adverse events compared to venlafaxine. Most common adverse events include nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and abnormal ejaculation/orgasm. It shares the same warning and precautions as venlafaxine in particular (eg, elevated blood pressure, mydriasis) and those of SSRIs, SNRIs (eg, suicide risk, serotonin syndrome, concomitant use with MAOIs). The cost of desvenlafaxine was not available at the time of this review.

Clinical Implications

Desvenlafaxine does not appear to offer any significant clinical advantage over venlafaxine which is available in generic form.

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CME Questions

13. Decreased levels of which of the following have been linked to increased risk of fractures for older men in recent studies?

a. free Testosterone
b. sex Hormone-Binding Globulin (SBHG)
c. estradiol (E2)
d. A) and B) above
e. all of the above

14. With regard to back pain and disability in health care workers and others who do heavy lifting:

a. There is robust evidence that both training and use of lifting devices prevent back pain and disability.
b. There is robust evidence use of lifting devices prevents back pain and disability, but training does not.
c. There is robust evidence that training prevents back pain and disability, but use of lifting devices does not.
d. There is no evidence that either training or use of lifting devices prevents back pain and disability.

Answers: 13 (a); 14 (d)

Clinical Briefs

By Louis Kuritzky, MD, *Clinical Assistant Professor, University of Florida, Gainesville*
Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Comprehensive Diabetes Care: The Whole Enchilada

THE GREATEST CHALLENGE FOR ANY potentially mortal disorder is to prove that therapeutic interventions reduce not only disease-specific mortality, but also all-cause mortality. For instance, PSA screening is associated with reduced prostate-cancer related mortality, but has never been convincingly shown to reduce all-cause mortality, leaving in question whether PSA screening results in some sort of mortality "trade-off," with no net benefit.

The Steno-2 Study enrolled type 2 diabetics with microalbuminuria (n=160) in 1993. Study subjects were randomized to intensive therapy (tight control of glucose, cholesterol, triglycerides, blood pressure, and microalbuminuria) or usual diabetic care. The study concluded after 8 years, at which point both groups and their clinicians were encouraged to employ intensive therapy post-trial.

In 2006 (five years after formal study closure), Gaede et al examined death from any cause comparing the two original study groups. The hazard ratio for all-cause mortality was 0.54 in the intensive treatment group (24 deaths vs 40 deaths), which included a 57% lesser chance of cardiovascular death, and a 59% lesser incidence of cardiovascular events.

Part of the intensive regimen included low-dose ASA and ACE (or ARB) for all, regardless of blood pressure. Although glucocentric focus in diabetes produces microvascular benefits, dealing with the "whole enchilada"-BP, lipids, the renin-angiotensin system, and platelets-increases the payoff for the patient. ■

Source: Goede P, et al. New Engl J Med. 2008;358:580-591.

The ENDORSE Study: Preventable Hospital Deaths

PULMONARY EMBOLISM (PUL-E) IS generally accepted as the most common preventable cause of in-hospital deaths in developed countries. As many as 10% of in-hospital deaths are attributable to PUL-E, hence prevention of venous thromboembolism is an epidemiologically compelling mandate. ENDORSE (Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting) is a chart audit of at-risk hospitalized patients to ascertain the rate of appropriate VTE thromboprophylaxis (TPX). Hospitals from 32 countries (including the US, UK, Germany and France) provided data on 68,183 hospital patients, categorically divided into surgical (45%) and medical (55%). American College of Chest Physicians (ACCP) guidelines were used to assess risk status and appropriateness of TPX.

Considering the entire study population, slightly over half (58.5%) of high-risk surgical patients, and less than half (39.5%) of the high-risk medical patients received appropriate TPX. Germany and Switzerland achieved distinctively higher levels of appropriate overall TPX (85% and 80%, respectively). With a few exceptions, the tendency to effectively prophylax medical patients less often than surgical patients was seen in all nations.

Reduced mortality through TPX for VTE is readily achievable, yet there remains an important gap between our potential to utilize VTE TPX and current practice worldwide. ■

Source: Cohen AT, et al. Lancet. 2008;371;387-394.

Risks of Stopping Clopidogrel

IN ADDITION TO ASPIRIN (ASA), clopidogrel (CPG) has demonstrated class 1A level evidence of its efficacy in acute coronary syndromes (ACS), and is typically continued for 1 year post-discharge. In ACS subjects it has been previously observed that at the time of cessation of antiplatelet therapies (ASA and heparin, for example), the risk of adverse cardiovascular (CV) events increases, suggesting a transient hyperthrombotic state, since this signal of increased events is not sustained. The authors sought to determine whether a CPG rebound effect occurs, as would be manifest by a cluster of CV events shortly after CPG discontinuation.

A cohort of VA hospital patients (n=3,137) post-discharge for ACS comprised the subjects for this retrospective cohort study. The study subjects were equally distributed between medically treated ACS and PCI treated patients. The incidence of MI and all-cause mortality was examined in the period 0-90 days, 91-180 days, and 181-270 days post CPG cessation.

Overall, there was a statistically significant increased risk of adverse CV events (1.82 relative risk) when comparing the immediate 0-90 day interval with the rest of the followup period. Both medically treated and PCI patients had similar outcomes.

This is the first study of its kind to specifically examine risk in the immediate CPG-cessation period. If confirmed, clinicians may have to rethink either the duration of CPG therapy, the discontinuation scheme (eg, down-titration, supplementary antiplatelet therapy), or both. ■

Source: Ho PM, et al. JAMA. 2008;299(5):532-539.

In Future Issues: **Smoking Quit Rates and Lung Age**