Sleep Apnea and Heart Disease -- Is the Relationship Strong?

Prospective Study of Obstructive Sleep Apnea and Incident Coronary Heart Disease and Heart Failure: The Sleep Heart Health Study.

Gottlieb DJ, Yenokyan G, et al:

Circulation 2010; 122 (July 27): 352-360

There is an association of heart failure and obstructive sleep apnea (OSA), but a weaker association of coronary heart disease and OSA; the association is strongest in older men and increases with increasing severity of OSA.

Background: Obstructive sleep apnea (OSA) has adverse cardiac effects. Data show a relationship between coronary heart disease (CHD) and OSA based on small, poorly controlled studies with few women. There are cross-sectional studies demonstrating a high incidence of OSA in patients with heart failure (HF), but no prospective studies on the association between OSA and incident HF.
Objective: To report the findings of a prospective community-based study of OSA and the incidence of CHD and HF.
Methods: Data were gathered from the Sleep Heart Health Study, a community-based, prospective, cohort study of the cardiovascular (CV) consequences of OSA in adults ≥40years old. Patients were recruited from existing studies of CV and pulmonary diseases and then asked to complete sleep habit questionnaires and undergo overnight polysomnography. Covariant data were derived from the primary cohort study from which the patient was recruited. From 1995 to 1998, 4422 of the 10,737 patients invited to participate were enrolled, completed an acceptable polysomnography study, were deemed to be without baseline cardiovascular disease, and had adequate follow-up data. Incident CHD was defined as first myocardial infarction, CHD death, or revascularization. HF was defined as first incidence of HF. Reported CHD and HF was further investigated by the parent cohort. Follow-up intervals were determined by the parent cohorts, but all patients were contacted within 12 months of the end of the study.
Results: 1927 men and 2495 women were followed for a mean of 8.7 years. Male gender, higher body mass index (BMI), lower HDL, higher systolic blood pressure, and a higher incidence of diabetes mellitus (DM) were all associated with OSA, as expected. Twenty-four percent of the men and 11% of the women had moderate-severe OSA, but after 5 years, only 5.5% had a physician diagnosis and only 2.1% were being treated. There were 473 incident cases of CHD and 308 incident cases of HF. Event rates increased with increasing severity of OSA. Once adjusted for covariates, there was not a statistically significant association between OSA and incident CHD, except in men ≤70 years of age with a hazard ratio (HR) of 1.10 per 10-unit increase in apnea-hypopnea index (AHI). When comparing those with AHI<5 to those with AHI ≥30, the HR was approximately 1.7. In adjusted models for HF, there remained an association between HF and OSA in men (HR, 1.13 per 10-unit increase in AHI) but not in women.
Conclusions: There is a relationship between OSA and incident HF in older men in the community, with a weaker relationship between OSA and incident CHD. Gender differences in OSA-related CV risk is suggested by these data.
Reviewer's Comments: This study in a community population suggests a weaker association between incident CHD and OSA than had previously been reported. It also emphasizes the likely gender differences in CV risk associated with OSA. (Reviewer-Karen Stout, MD).

Keywords: Obstructive Sleep Apnea, Coronary Heart Disease, Heart Failure, Women

Print Tag: Refer to original journal article

Women and Men Are Also Different When It Comes to Heart Rate

Heart Rate Response to Exercise Stress Testing in Asymptomatic Women: The St. James Women Take Heart Project.

Gulati M, Shaw LL, et al:

Circulation 2010; 122 (July 13): 130-137

Chronotropic incompetence predicts all-cause mortality in women, but the standard calculation overestimates the maximum heart rate for age in women.

Background: The heart rate (HR) response to exercise in women is not clearly defined. Inadequate HR response is known to be a poor prognostic indicator with exercise testing, but the norms on which the definition of inadequate are based were defined in men.
Objective: To define the normal HR response to exercise in women and evaluate a variety of HR measures to determine prognostic ability for all-cause and cardiac mortality.
Participants/Methods: 5932 asymptomatic women volunteered to undergo stress testing as part of the St. James Women Take Heart project in Chicago. Participants were ≥35 years of age and were excluded if pregnant, had angina symptoms, had a myocardial infarction, weighed >325 pounds, or were hypertensive. Framingham Risk Scores were derived, and stress tests were symptom-limited on a standard Bruce protocol. Multiple measures of chronotropic response were evaluated, including the absolute HR after stage 2, absolute peak HR, HR reserve (defined as peak HR minus resting HR), peak HR compared to the mean for age in the cohort, ability to achieve 85% of target HR, and a chronotropic index (which has been described previously). Deaths were determined by the Social Security Death Index.
Results: 5437 women met inclusion criteria; their mean age was 52 years, and the mean follow-up was 15.9 years, with 10% mortality over the period. Maximal HR decreased with age, with few women (7%) failing to meet 85% target HR based on standard criteria but 25% exceeding 100% maximum HR. Women who had a chronotropic index <0.8 were older, had a higher body mass index, were more likely hypertensive and smokers, and had higher Framingham Risk Scores. The women with normal chronotropic response had higher peak exercise capacity, but also had more exercise-induced angina than did women with chronotropic incompetence. The ability to achieve 85% of age-predicted HR was not a predictor of mortality, but a chronotropic index <0.8 or HR ≥1 SD below the mean for the age group were associated with higher mortality. The traditional estimate of HR maximum overestimated the maximal HR in women.
Conclusions: Standard HR estimates overestimate the maximal exercise HR in women. Gender-specific physiologic HR response parameters should be incorporated into standard exercise assessment and clinical practice.
Reviewer's Comments: The seemingly simple question of a normal HR response to exercise in women had not previously been addressed, and given the number of prognostic data that derive from HR response, this is an overdue study. The parameters described, along with the norms, should be incorporated into clinical practice. (Reviewer-Karen Stout, MD).

Keywords: Women, Exercise Stress Test, Heart Rate

Print Tag: Refer to original journal article

What You Eat Really Does Matter

Major Dietary Protein Sources and Risk of Coronary Heart Disease in Women.

Bernstein AM, Sun Q, et al:

Circulation 2010; 122 (August 16): 876-883

Changing dietary protein sources from red meat to poultry, low-fat dairy, or nuts reduces the risk of coronary artery disease in women.

Background: There is evidence that substituting poultry or fish for red meat can decrease the risk of incident coronary artery disease (CAD). However, relatively little data exist about the impact of other protein sources on incident CAD and the impact over a substantial follow-up period.
Objective: To examine the relationship between different dietary protein sources and incident CAD in women over 26 years of follow-up.
Methods: The data for this report were derived from the Nurse's Health Study, which included >121,000 nurses from 30 to 55 years of age, and began collecting data in 1976. In 1980, a validated food frequency questionnaire (FFQ) was added to the biennial data collection, and in 1984, it was expanded to include more foods. Just over 84,000 women who completed the FFQ fully, who reported plausible daily caloric intake, and who did not have preexisting malignancy or heart disease were included in this analysis. Protein sources were either meat or dairy and were broken down by type of meat (beef, processed meat, lamb, fish, etc) or dairy (whole or skim milk, cottage cheese, etc). The primary end point was nonfatal myocardial infarction (MI) or fatal CAD occurring between 1980 and 2006. FFQ data collection stopped at either an intermediate CAD risk diagnosis (such as diabetes) or with the diagnosis of malignancy, stroke, or coronary bypass since those diagnoses would be expected to generate dietary changes. MI was defined in the usual fashion, and deaths were determined by the National Death Index.
Results: There were >2 million person-years of follow-up, with 2210 MIs and 952 deaths. High consumption of red meat was associated with higher rates of smoking, hypertension, angina, sedentary lifestyle, diabetes, increased trans-fat intake, and lower intake of vitamin E/multivitamins. In unadjusted and adjusted models, higher intakes of red meat, red meat excluding processed meat, and high-fat dairy products were associated with higher CAD risk, while higher intake of poultry, fish, and nuts was associated with a lower CAD risk. In models controlling for energy intake, compared to 1 serving of meat, there was a 30% risk reduction for 1 serving of nuts, a 13% risk reduction with 1 serving of low-fat dairy, 19% for poultry, and 24% for fish.
Conclusions: Red meat intake increases the risk of CAD, and shifting dietary protein sources could reduce CAD risk.
Reviewer's Comments: This study demonstrates that there is a benefit in women to decrease the amount of red meat consumption. However, this also demonstrates that one does not need to become a vegetarian, but shifting intake from red meat to other dietary proteins like poultry, fish, nuts, and low-fat dairy can reduce the risk of CAD. This may be an effective change in the U.S. diet to effect a reduction in CAD risk. (Reviewer-Karen Stout, MD).

Keywords: Diet, Coronary Risk, Women, Protein Sources

Print Tag: Refer to original journal article

Exercise Is Good for You Regardless of Your Age

Exercise Capacity and Mortality in Older Men: A 20-Year Follow-Up Study.

Kokkinos P, Myers J, et al:

Circulation 2010; 122 (August 24): 790-797

There is a graded and inverse relationship between exercise capacity and all-cause mortality in all ages of men >65 years old.

Background: Fitness status and mortality are inversely associated in both apparently healthy subjects and those with cardiovascular disease (CVD). Despite robust data in middle-aged people, little data exceed on the impact of fitness on mortality in people >65 years of age, particularly data that include objective exercise testing.
Objective: To report on a study of the relationship between mortality and exercise capacity in men >65 years of age.
Methods: Veterans >65 years of age who underwent exercise testing (ETT) were enrolled. Those with pacemakers, left bundle branch block with exercise, heart failure, a positive exercise test, or hemodynamic instability during ETT were excluded. Usual cardiovascular risks and diseases, as well as medications, were assessed through a review of the electronic medical record and confirmed with the patient. Deaths were identified through the Social Security Death Index and the Veterans Affairs Beneficiary Identification and Record Locator system file. Exercise testing was by standard treadmill protocols with fitness levels determined by the number of metabolic equivalents (METS) achieved.
Results: 5314 men (mean age, 71 years) were divided into 2 categories, those 65 to seventy years old (n=2560) and those >70 years (n=2750). The median follow-up time was 8.1 years, and there were 2137 deaths. Adjusted models for the entire cohort demonstrated a 12% lower mortality for each 1 MET increase in exercise capacity, with increased mortality associated with diabetes mellitus, smoking, CVD, and body mass index (BMI). When evaluating the 2 age groups separately, comparing those who had poorer fitness (≤4 METS) with those who were more fit (>5 METS), there was a 32% to 65% lower mortality in the 65 to 70 age group and a 45% to 60% lower mortality in those >70 years. The authors accounted for reverse causality in several ways, attempting to ensure that fitness was not a reflection of underlying diseases that would affect mortality. Those who were excluded included patients who died within the first 2 years of follow-up, those with chronotropic incompetence, and those with a BMI<20 who were in the lowest fitness groups. These adjustments did not change the association between mortality and exercise capacity. The study evaluated 867 patients who had a second ETT and grouped them based on fitness on both tests. The lowest mortality was seen in those who were fit and remained so. However, those who were unfit and became fit had a 35% lower mortality than those who remained unfit at both examinations.
Conclusions: Exercise capacity is an independent inverse and graded predictor of all-cause mortality in men >65 years of age. Survival was highest in those who achieved >5 METS on a standard exercise protocol, and for unfit individuals who became fit, survival improved.
Reviewer's Comments: These data show that fit older individuals, like younger people, have a survival benefit. The improved survival in unfit people who become fit is an additional argument for ensuring our unfit patients, regardless of age, get in shape. (Reviewer-Karen Stout, MD).

Keywords: Exercise Capacity, Mortality

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Bystander CPR -- Rescue Breathing or Chest Compressions Alone?

CPR With Chest Compression Alone or With Rescue Breathing.

Rea TD, Fahrenbruch C, et al:

N Engl J Med 2010; 363 (July 29): 423-433

There is no significant difference in survival between bystander CPR patients who receive chest compressions alone and those who also receive rescue breathing.

Objective: To determine whether emergency medical service (EMS) dispatcher instructions to perform chest compressions only would improve survival compared to compressions plus rescue breathing.
Design: Randomized trial.
Participants: 1941 adults who suffered out-of-hospital cardiac arrests in King County, Washington, Thurston County, Washington, and London and were not already receiving cardiopulmonary resuscitation (CPR) when EMS dispatchers were called.
Methods: At the time of the call for assistance, if the caller was willing to undertake CPR, dispatchers opened a randomization envelope and instructed the bystander to either perform chest compressions only or rescue breaths plus chest compressions at a ratio of 2:15. The primary outcome measured was survival to hospital discharge.
Results: 5525 randomization envelopes were opened during the study, but the majority of patients were subsequently excluded because paramedics found them to be either alive without evidence of cardiac arrest or to have signs of irretrievable death. Seventy percent of the eligible patients had arrests with a primary cardiac cause, and one-third had a shockable rhythm. The average EMS response time was 6.5 minutes. There was no significant difference in survival to hospital discharge, which was 12.5% for patients in the chest compressions group and 11% in the chest compressions plus rescue breathing group. Among those with a primary cardiac cause of arrest, there was a trend toward improved survival with compressions alone (15.5% vs 12.3% for those with other causes). In the patients with a shockable rhythm, survival was 31.9% with chest compressions alone versus 25.7% with compressions plus rescue breathing. Neurologic outcomes were also similar with the 2 strategies.
Conclusions: Overall, survival was similar when bystanders were instructed to perform chest compressions only or compressions plus rescue breathing. In patients thought to have a cardiac cause of arrest and those with a shockable rhythm, there was a trend toward improved survival with chest compressions alone.
Reviewer's Comments: When bystanders were instructed to do compressions only, the patient was more likely to receive compressions than when the bystander was asked to do compressions plus breathing (80% vs 72%). This points to one of the advantages of bystander compression-only CPR—it is more likely to be acceptable to the average man on the street. (Reviewer-Karen A. McDonough, MD).

Keywords: Cardiopulmonary Resuscitation, Rescue Breathing, Chest Compressions

Print Tag: Refer to original journal article

Simplified PESI Is Easier to Remember and Use

Simplification of the Pulmonary Embolism Severity Index for Prognostication in Patients With Acute Symptomatic Pulmonary Embolism.

Jiménez D, Aujesky D, et al:

Arch Intern Med 2010; 170 (August 9): 1383-1389

A greatly simplified Pulmonary Embolism Severity Index performs as well as the original in categorizing patients as low or high risk for 30-day mortality.

Background: The Pulmonary Embolism Severity Index (PESI) is an extensively validated clinical prediction rule for 30-day mortality in acute pulmonary embolism (PE). The downside of the PESI is that it has 11 different variables that are assigned different weights making it challenging to remember it or use it in a busy emergency department (ED) or clinic.
Objective: To develop a simplified PESI and compare its performance with the original.
Design: Prospective cohort study.
Participants/Methods: The derivation cohort consisted of all outpatients with confirmed PE at a single Spanish hospital from 2003 to 2008. The simplified PESI was validated using the first 7106 outpatients with acute PE enrolled in an ongoing international registry of patients with venous thromboembolism.
Results: In the derivation cohort, 4 variables in the original PESI had no significant association with 30-day mortality and were dropped from the index. These were male sex, respiratory rate >30, altered mental status, and temperature <36°. The remaining variables were each assigned 1 point: age >80 years; history of cancer; history of heart failure or chronic lung disease; pulse ≥110 beats/minute; systolic blood pressure <100 mm Hg; and oxyhemoglobin saturation level <90%. Patients receiving 0 points were categorized as low risk and those with ≥1 point as high risk. The prognostic accuracy of the simplified PESI was as good as the original. Forty percent of the patients were classified as low risk by the original PESI as were 36% with the simplified version. In the simplified PESI validation cohort, the 30-day mortality of the low-risk group was 1.1% and 8.9% in the high-risk group. This compares with 2.5% 30-day mortality in the original PESI low-risk group and 14% in the high-risk patients.
Conclusions: The simplified PESI performs as well as the original and is easier to remember and use.
Reviewer's Comments: The take home message is that easy to remember variables identify patients at higher mortality risk. Any of the variables of tachycardia, hypotension, hypoxia, underlying cancer, heart failure or pulmonary disease, and age >80 years means a patient is high risk and should be hospitalized rather than discharged on low molecular weight heparin. (Reviewer-Karen A. McDonough, MD).

Keywords: Pulmonary Embolism, Mortality, Clinical Prediction Rule

Print Tag: Refer to original journal article

The Downside of IVC Filters

Prevalence of Fracture and Fragment Embolization of Bard Retrievable Vena Cava Filters and Clinical Implications Including Cardiac Perforation and Tamponade.

Nicholson W, Nicholson WJ, et al:

Arch Intern Med 2010; August 9 (): epub ahead of print

A Food and Drug Administration-approved retrievable inferior vena cava filter currently in use has a 12% prevalence of strut fracture after a mean of 24 months, with potential for embolization.

Background: Fracture and embolization is a rarely reported complication of inferior vena cava (IVC) filters.
Objective: After caring for a patient with cardiac tamponade caused by a fractured IVC filter strut, the authors assessed the prevalence of fractures in 2 models of retrievable filters: the Bard Recovery filter, which was available from 2003 to 2005, and the redesigned Bard G2 filter, available from 2005 to the present.
Design: Retrospective cohort study.
Participants: Patients who had Bard Recovery or Bard G2 filters placed at a single hospital from April 2004 to January 2009 were evaluated. Among the 189 total patients receiving the filters, 35 had died, 10 had had the filter removed, and 59 could not be contacted; 80 patients agreed to have fluoroscopy to assess their filters for fracture.
Methods: All patients had fluoroscopy of the device. Those with evidence of fracture had further fluoroscopy to determine where any fragments ended up. Those with intracardiac fragments all had transthoracic echoes, and selected patients had cardiac CT to define the exact location of fragments.
Results: Overall, 16% of patients had at least 1 strut fracture: 25% of those with the older Recovery filter (in place for a mean of 50 months) and 12% of those with the redesigned G2 filter (in place for a mean of 24 months). Five of the 7 patients with a fractured Recovery filter had at least 1 fragment in the right ventricle. In 4 of the 6 patients with G2 filter fractures, fragments were still in the IVC. The G2 filter fragments embolized to the hepatic artery in 1 patient and the lung in 1 patient. Six different physicians from 3 different specialties implanted the devices that fractured.
Conclusions: These 2 models of IVC filter have a high prevalence of fracture, likely due to metal fatigue. The institution where the study was performed has stopped implanting these filters.
Reviewer's Comments: Although these filters are retrievable, only 10 of the 189 devices implanted at 1 hospital were actually removed, which the authors report is similar to the experience at other institutions. They raise the concern that the lower fracture prevalence seen with the newer filter may be due to the shorter mean time these devices have been in place rather than the change in design. Prior to the availability of retrievable devices, I was hesitant to recommend placement of an IVC filter because of the long-term risk of thrombosis and embolization of clot. Some of the filters I have recommended (based on very limited published data) have stayed in place for a variety of reasons. After reading this article, my threshold for recommending an IVC filter has gone way up again. (Reviewer-Karen A. McDonough, MD).

Keywords: Venous Thromboembolism, Inferior Vena Cava Filter

Print Tag: Refer to original journal article

Extended-Duration VTE Prophylaxis for Medical Patients -- Not Quite Yet

Extended-Duration Venous Thromboembolism Prophylaxis in Acutely Ill Medical Patients With Recently Reduced Mobility: A Randomized Trial.

Hull RD, Schellong SM, et al:

Ann Intern Med 2010; 153 (July 6): 8-18

Extended-duration venous thromboembolism (VTE) prophylaxis after hospital discharge for acutely bedridden patients (especially those age >75 years or women) may decrease VTE incidence but at the cost of increased risk of major hemorrhage.

Background: Venous thromboembolism (VTE) prophylaxis reduces VTE in many hospitalized medical and surgical patients. Extending inpatient VTE prophylaxis to the outpatient setting benefits some high-risk surgical patients (ie, hip/knee replacement). It is unclear if high-risk medical patients might also benefit from extended-duration VTE prophylaxis.
Objective: To evaluate the efficacy and safety of extended-duration enoxaparin VTE prophylaxis in acutely ill medical patients after hospital discharge.
Design/Participants: This randomized, multicenter (20 countries), controlled trial sponsored by the manufacturer of enoxaparin enrolled 5963 acutely ill medical patients ≥40 years old with recently reduced mobility defined as bed rest or sedentary without bathroom privileges (level 1) or sedentary with bathroom privileges (level 2). Participants had reduced mobility for up to 3 days prior to, and expected for ≥3 days after, enrollment. Because interim analyses suggested lower than expected VTE rates, eligibility criteria for level 2 patients were changed part way through the study to include only those with the additional VTE risk factors of age >75 years, history of VTE, or active/previous cancer.
Methods: All participants received subcutaneous enoxaparin 40 mg daily for approximately 10 days initially and were then randomized to placebo versus continued enoxaparin at the same dose for approximately 28 more days. The primary end point was VTE incidence (composite of symptomatic and asymptomatic proximal deep venous thrombosis [DVT] or symptomatic pulmonary embolism) during the double-blind portion of study. Asymptomatic proximal DVTs were identified via ultrasonography of legs at the end of the double-blind treatment period. Another primary outcome measure was incidence of major bleeding (decrease in hemoglobin by ≥20 g/L, transfusion of ≥2 units blood, bleeding requiring surgery, retroperitoneal, intracranial or intraocular bleeding, or death from bleeding) up to 48 hours after the last study drug dose. The secondary end point was mortality at 1, 3, and 6 months.
Results: Extended-duration enoxaparin reduced VTE incidence compared with placebo (2.5% vs 4%), with most benefit due to reduction in symptomatic proximal DVT. Extended-duration enoxaparin also increased major bleeding events (0.8% vs 0.3%) compared to placebo. The benefit of extended-duration enoxaparin was only present in women, persons >75 years of age, and those with level 1 immobility. There were no differences in mortality.
Conclusions: Extended-duration enoxaparin reduces VTE more than it increases major bleeding in acutely ill medical patients with level 1 immobility, those >75 years old, and women.
Reviewer's Comments: Unfortunately for the manufacturer of enoxaparin, this study fails to convince me that extended VTE prophylaxis is a good idea. The change in inclusion criteria during the study, the subgroup analyses needed to parse out a group of patients who might benefit from the intervention, and the minimal reported benefits dissuade me and do not overcome my concerns about cost, drug administration, monitoring, and hemorrhage risk that extended VTE prophylaxis with enoxaparin would involve. (Reviewer-Melissa Hagman, MD).

Keywords: Extended-Duration Venous Thromboembolism, Prophylaxis, Enoxaparin

Print Tag: Refer to original journal article

Increased Cardiovascular Risk With Testosterone Administration

Adverse Events Associated With Testosterone Administration.

Basaria S, Coviello AD, et al:

N Engl J Med 2010; 363 (July 8): 109-122

A randomized controlled trial of testosterone administration in hypogonadal, mobility-limited elderly men showed an increased risk of cardiovascular events.

Background: Limited mobility in elderly patients predicts disability and death. In aging men, low testosterone (T) levels are associated with declines in muscle mass, lower extremity strength, and mobility. T supplementation of hypogonadal men increases muscle mass and strength, although previous studies have been in men without significant mobility impairment.
Objective: To evaluate the safety and efficacy of T administration in hypogonadal elderly men with impaired mobility.
Design: Randomized, placebo-controlled, double-blind trial.
Participants/Methods: Eligible subjects were ≥65 years of age and had serum T levels between 100 and 350 ng/dL or free T levels of <50 pg/mL. All subjects had impaired mobility, defined as difficulty walking 2 blocks on level ground or climbing 10 steps. Exclusion criteria were appropriate, including severe cardiovascular disease. Subjects were randomized to daily 1% T gel titrated to a plateau serum T concentration of 500 to 1000 ng/dL or placebo and were followed for 6 months. The primary outcome was a quantitative measure of lower extremity strength.
Results: Enrollment was halted by the data and safety monitoring board because of concern for an excess of cardiovascular adverse events (AEs) in the testosterone group than in the placebo group. A total of 209 of a planned 252 men had been enrolled, and 176 men had completed at least 12 weeks of T. The average age was 74 years; almost half had pre-existing cardiovascular disease, and obesity, hypertension, hyperlipidemia, and diabetes were prevalent. There was a significant increase in hematocrit levels and a decrease in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels in the group treated with T, as has been seen in previous studies. Significantly more men in the T group reported ≥1 AEs. Serious and life-threatening AEs were more common in the T group. A total of 30 men had cardiovascular-related or atherosclerosis-related AEs compared to 6 in the placebo group. The increased risk of AEs remained after adjusted for known cardiovascular risk. Men in the highest quartile of serum T on treatment had a more than 2-fold increase risk compared with other subjects. Leg strength improved in men treated with T.
Conclusions: Testosterone supplementation in older, mobility-impaired, hypogonadal men with prevalent baseline cardiovascular risk factors was associated with an increased risk of cardiovascular events.
Reviewer's Comments: Although previous studies of T supplementation in hypogonadal men have suggested that it is safe and effective, this trial raises the specter of increased cardiovascular risk. It may well be that patients with impaired mobility are at particularly high cardiovascular risk. The authors make the important points that the observed AEs, although undeniably of concern, were small in number and varied in terms of severity and pathogenesis; the observed difference may have been due to chance. (Reviewer-Paul R. Sutton, PhD, MD).

Keywords: Testosterone Deficiency, Supplementation, Cardiovascular Risk

Print Tag: Refer to original journal article

Risks of Bariatric Surgery Lower at Centers With Higher Surgical Volume

Hospital Complication Rates With Bariatric Surgery in Michigan.

Birkmeyer NJO, Dimick JB, et al:

JAMA 2010; 304 (July 28): 435-442

Bariatric surgery risks are low, but they are not zero.

Background: As the incidence of obesity increases, more and more patients are considering bariatric surgery. The short-term complications vary by procedure type, but do they vary based on surgeon experience or whether the hospital is a center of excellence (COE) in bariatric surgery? The COE designation is an accreditation based in part on resources and visit volumes.
Objective: To examine the bariatric surgery perioperative complications at 25 hospitals in Michigan and assess the effect of procedure volume and COE designation.
Design: Prospective chart review.
Methods: The Michigan Bariatric Surgery Collaborative (MBSC) is a voluntary, payer-funded clinical outcomes registry that currently enrolls patients from 25 hospitals in Michigan. All patients in the MBSC undergoing first bariatric surgery from June 2006 through September 2009 were identified. Patients undergoing duodenal switch procedure were excluded. Complications occurring within 30 days of surgery were identified and grouped into non–life-threatening, potentially life-threatening, and life-threatening. Potentially life-threatening complications included those requiring drainage or reoperation, short-term dialysis, intubation for 2 to 7 days, transfusion >4 units, or deep venous thrombosis. Life-threatening complications included death, cardiac arrest/myocardial infarction, long-term dialysis, or intubation >7 days. The main outcome was complications based on procedure type, procedure volumes, and COE designation.
Results: 15,275 patients (average age, 46 years; average body mass index, 46) were included in the analysis. Patients undergoing laparoscopic adjustable gastric band (lap band) had fewer comorbidities than patients undergoing sleeve gastrectomy or gastric bypass. Seven percent of patients had at least 1 complication. Potentially life-threatening complications were uncommon: 0.78% with lap band; 2.2% with sleeve gastrectomy; and 3.1% with gastric bypass. Life-threatening but not fatal complications occurred in 0.04% of lap band patients and 0.33% of gastric bypass patients. Two patients (0.04%) undergoing lap band and 13 patients (0.14%) undergoing gastric bypass died in the perioperative period. Serious complication rates (potentially life-threatening and life-threatening) declined as patient volume increased. There was no difference in complication rates between COE and non-COE hospitals.
Conclusions: The rates of serious complications following bariatric surgery are low and are inversely related to the hospital surgical volume. The designation as a COE in bariatric surgery does not translate to better surgical outcomes.
Reviewer's Comments: Surgical treatment for obesity has been shown to slow progression of chronic disease as well as prolong life. But as this study demonstrates, although the risk is low, it is not zero. Our goal should continue to be education to reduce obesity. When needed, patients should be referred to surgical centers with high patient volumes to minimize their perioperative risk. (Reviewer-Deborah L. Greenberg, MD).

Keywords: Bariatric Surgery, Complication Rates, Center of Excellence, Procedure Volume

Print Tag: Refer to original journal article

GH Influences Body Composition, Increases Sprint Capacity

The Effects of Growth Hormone on Body Composition and Physical Performance in Recreational Athletes: A Randomized Trial.

Meinhardt U, Nelson AE, et al:

Ann Intern Med 2010; 152 (May 4): 568-577

Growth hormone influences body composition and increases sprint capacity in healthy recreational athletes.

Background: Illicit use of growth hormone (GH) is reportedly widespread among competitive athletes, but its effect on physical performance has never been demonstrated in a scientific study.
Objective: To determine the effect of GH on body composition and physical performance.
Design: Randomized, blinded, placebo-controlled trial.
Participants/Methods: 96 healthy recreational athletes (34% women) aged 18 to 40 years (mean, 28 years) who had engaged in at least 2 weekly workout sessions for the past year were recruited. All patients were randomly assigned to GH or placebo; men were also randomly assigned to testosterone or placebo. Patients received study drugs for 8 weeks and were then followed during a 6-week washout period. The main outcome measures were body composition (fat mass, lean body mass, extracellular water, and body cell mass) and physical performance (maximum oxygen consumption [VO_2] max, dead-lift, vertical leap, and total work during sprint cycle ergometry). The study was funded by The World Anti-Doping Agency.
Results: GH significantly decreased fat mass, increased extracellular water, and, when combined with testosterone in men, increased body cell mass. VO_2 max, dead-lift strength, and vertical leap did not improve, but sprint capacity increased by 0.71 kJ (95% CI, 0.1 to 1.3 kJ; relative increase, 3.9%). In men who also received testosterone, sprint capacity increased by 1.7 kJ (relative increase, 8.3%). The effect on sprint capacity was no longer observed 6 weeks after GH supplementation ended. Swelling (66%) and joint pain (47%) were significantly more common with GH than placebo. Paresthesias (28%) were also common but not quite statistically significant. Overall, 84% of GH recipients reported an adverse event.
Conclusions: GH supplementation influenced body composition and increased sprint capacity in healthy recreational athletes.
Reviewer's Comments: This is the first scientific study to demonstrate a change in physical performance with GH. The GH dosage used is thought to be much lower than that taken by elite athletes, and the competitive significance of the increase in sprint capacity demonstrated is unknown. The authors explain that GH may increase sprint capacity via more efficient energy extraction during anaerobic metabolism. I enjoyed learning about a topic that has been widely discussed in the popular press, but, clearly, the practical importance of this trial is very limited. My personal experience with prescribing a Food and Drug Administration-approved formulation of recombinant GH to a patient with HIV-associated wasting was to observe side effects similar to those documented here. (Reviewer-John V.L. Sheffield, MD).

Keywords: Growth Hormone, Body Composition, Physical Performance

Print Tag: Refer to original journal article

Rosiglitazone Increases Risk of Stroke, Heart Failure, Death

Risk of Acute Myocardial Infarction, Stroke, Heart Failure, and Death in Elderly Medicare Patients Treated With Rosiglitazone or Pioglitazone.

Graham DJ, Ouellet-Hellstrom R, et al:

JAMA 2010; 304 (July 28): 411-418

Compared to treatment with pioglitazone, treatment with rosiglitazone in diabetic patients is associated with an increased risk of stroke, heart failure, and death.

Background: The 2 available thiazolidinedione agents, pioglitazone and rosiglitazone, have similar effects on glycemic control, but prior studies indicate that they may have different cardiovascular risk profiles. Whereas both agents can increase the risk of heart failure, meta-analyses have shown reduced risk of acute myocardial infarction (MI), stroke, and all-cause mortality with pioglitazone while rosiglitazone increased the risk of these adverse outcomes.
Objective: To determine whether treatment with rosiglitazone increases cardiovascular risk compared with treatment with pioglitazone.
Design: Retrospective cohort study.
Methods: The nationwide Medicare Part D prescription database was used to identify an inception cohort of 227,571 patients aged ≥65 years (mean age, 74 years) who initiated treatment with rosiglitazone (n=67,593) or pioglitazone (n=159,978) from July 2006 to June 2009. The main outcome measures were acute MI, stroke, heart failure, and all-cause mortality.
Results: Baseline characteristics were similar between patients treated with pioglitazone and rosiglitazone. As compared with pioglitazone, rosiglitazone did not increase the risk of acute MI (adjusted hazard ratio [AJR], 1.06; 95% CI, 0.96 to 1.18) but did increase the risk of stroke (AJR, 1.27; 95% CI, 1.12 to 1.45), heart failure (AJR, 1.25; 95% CI, 1.16 to 1.34), and all-cause mortality (AHR, 1.14; 95% CI, 1.05 to 1.24). The number of patients who would need to be treated with rosiglitazone for 1 year to cause cardiovascular harm to 1 person was 60.
Conclusions: Compared to treatment with pioglitazone, treatment with rosiglitazone was associated with an increased risk of stroke, heart failure, and all-cause mortality.
Reviewer's Comments: This study utilized the nationwide Medicare Part D prescription database to identify a large cohort of patients who are representative of the general U.S. population. Although the findings are subject to the limitations of all cohort studies, the baseline characteristics of the 2 treatment groups were remarkably similar. Therefore, confounding seems an unlikely explanation for the results. Evidence continues to mount that rosiglitazone's cardiovascular risk profile is substantially worse than pioglitazone's profile. In diabetic patients who require treatment with a thiazolidinedione, there seems to be no reason to choose rosiglitazone over pioglitazone. (Reviewer-John V.L. Sheffield, MD).

Keywords: Thiazolidinedione, Diabetes, Treatment, Adverse Effects

Print Tag: Refer to original journal article

Calcium Plus Vitamin D Does Not Increase Risk of Heart Attack

Calcium/Vitamin D Supplementation and Coronary Artery Calcification in the Women's Health Initiative.

Manson JE, Allison MA, et al:

Menopause 2010; 17 (July): 683-691

Calcium taken with vitamin D does not increase the prevalence of coronary calcifications in postmenopausal women.

Background: Calcium supplementation is widely recommended to prevent or treat osteopenia and osteoporosis. There has been recent concern that the intake of calcium without vitamin D may increase the risk of heart disease in postmenopausal women. This finding has not been universal and other studies suggest that the addition of vitamin D may mitigate this potential risk. Studies of cardiovascular disease can be difficult to do if the expected event rate is low. Coronary artery calcification (CAC) scores are often used as a surrogate measure because they have been shown to predict future cardiovascular events.
Objective: To assess the association between calcium and vitamin D supplementation and CAC in postmenopausal women.
Design: Double-blind, placebo-controlled, randomized trial.
Methods: Participants in the Women's Health Initiative- Coronary Artery Calcium Study (WHI-CACS) were invited to participate in a randomized calcium and vitamin D trial. Women were aged 50 to 59 years at initial enrollment, had undergone hysterectomy, were previously randomized to conjugated equine estrogen (CEE) or placebo, and were subsequently randomized to calcium 1,000 mg a day and vitamin D 400 IU per day or placebo. Coronary CT scans were performed at the end of the trial period. The primary outcome was CAC score in the calcium/vitamin D group compared to the placebo group after adjusting for cardiac risk factors and CEE assignment. CAC scores were divided into 4 groups: none (0); mild (1 to 100); moderate (101 to 300); and extensive (>300).
Results: 754 women were included in the analysis. The average intervention time was 7 years, and the average age was 64.8 years at the time of CAC evaluation. There was no difference in the CAC scores between the 2 groups. The mean score was 91.6 in those taking calcium/vitamin D and 100.5 in those on placebo. The distribution in CAC score categories was similar in the 2 groups.
Conclusions: Postmenopausal women randomized to calcium and vitamin D supplementation for 7 years have similar presence and extent of coronary calcifications as women randomized to placebo.
Reviewer's Comments: Previously published results from the WHI showed no association between cardiovascular events and calcium/vitamin D supplementation in >36,000 postmenopausal women. This study looking at CAC in a subset of these patients suggests that their future cardiovascular risk is not increased compared to women taking placebo. Calcium supplementation when taken with vitamin D appears to be safe and should continue to be used for prevention and treatment of osteoporosis. (Reviewer-Deborah L. Greenberg, MD).

Keywords: Calcium, Vitamin D, Supplements, Coronary Artery Calcification

Print Tag: Refer to original journal article

Vertebroplasty Reduces Pain Compared to Conservative Care

Vertebroplasty Versus Conservative Treatment in Acute Osteoporotic Vertebral Compression Fractures (Vertos II): An Open-Label Randomised Trial.

Klazen CAH, Lohle PNM, et al:

Lancet 2010; August 9 (): epub ahead of print

In patients with acute osteoporotic vertebral compression fractures, vertebroplasty reduces pain compared to conservative care with analgesics, but it is unclear if it is better than injection of local anesthetic.

Background: Percutaneous vertebroplasty has been widely used for treatment of vertebral compression fractures despite mixed evidence of benefit.
Objective: To clarify whether vertebroplasty provides any additional value compared to optimum pain treatment in patients with acute vertebral fractures.
Design: Randomized intervention trial with usual care control and open allocation.
Participants: Patients ≥50 years of age with osteopenia, a vertebral compression fracture on x-ray, visual analog pain score ≥5, MRI findings of bone edema consistent with a fracture, point tenderness on examination, and <6 weeks of pain were included. Patients with radiculopathy or cord compression or with contraindications for MR imaging were excluded, as were those with coagulopathies, infection, and suspicion of underlying malignancy.
Methods: Patients randomized to vertebroplasty had their fractured vertebrae injected with cement via two 11- or 13-gauge needles under fluoroscopic guidance. Patients with multiple fractures on MRI had all fractures treated as part of the protocol. The primary outcome was pain relief at 1 month and 1 year, with secondary outcomes of cost-effectiveness and analgesic use.
Results/Conclusions: At 1 day after vertebroplasty, the mean pain score (out of 10) in the vertebroplasty group was 3.7 versus 6.7 in the conservative group. At 1 year, vertebroplasty patients still had a mean pain score of 2.2 versus 3.8 in the conservative group. Not surprisingly, the vertebroplasty group had more procedural complications: Nearly 75% had some degree of cement leakage, although none involved the spinal canal. One patient showed fluoroscopic cement migration into the venous system that went to the lung, but without any symptoms or long-term effects. The secondary end point analysis showed reduction in medication use and improvement in quality of life in the vertebroplasty group. The estimated cost-effectiveness was approximately $30,000 in U.S. currency per quality-adjusted life-year gained.
Reviewer's Comments: This will undoubtedly be a controversial study. There have been several large controlled trials of vertebroplasty and kyphoplasty published at this point, and the common theme is that those with an invasive sham control, such as injection of saline or anesthetic, did not show significant differences in outcome between treatment and control groups, while those with a conservative, noninvasive control group did. I think that counseling about vertebroplasty should include discussion of risks and costs of the procedure as well as possible benefits, and that we should disclose that sham controlled trials have not been able to demonstrate benefits of the procedure, as a well-informed patient may well discover this on their own. For patients who feel strongly that they want to "do something" about the problem, vertebroplasty may be helpful. For patients who would prefer to avoid needles and cement, it is easy to argue that the studies are inconclusive. (Reviewer-Christopher L. Knight, MD).

Keywords: Osteoporosis, Vertebral Fracture, Vertebroplasty, Conservative Treatment

Print Tag: Refer to original journal article

Naltrexone Plus Bupropion Helps With Weight Loss for Some

Effect of Naltrexone Plus Bupropion on Weight Loss in Overweight and Obese Adults (COR-I): A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial.

Greenway FL, Fujioka K, et al:

Lancet 2010; 376 (August 21): 595-605

Combination therapy with naltrexone plus bupropion helps moderately obese patients lose weight.

Background: Obesity is a problem of extraordinary magnitude, and its prevalence is growing. The neuroendocrine pathways of obesity have led to increased interest in examining it from the point of view of addiction.
Design: Randomized, placebo-controlled, double-blind trial.
Participants/Methods: This manufacturer-sponsored trial enrolled 1742 participants between the ages of 18 and 65 years with a body mass index (BMI) between 30 and 45. Patients were allowed to enroll with a BMI down to 27 if they had dyslipidemia or hypertension. Patients with diabetes, cardiovascular disease, liver disease, renal disease, prior bariatric surgery, history of seizures or serious psychiatric illness, prior treatment with the study drug, a history of drug or alcohol use in the past year, and weight fluctuation of >4 kg in the prior 3 months were all excluded from the study. They did not allow the use of other weight loss drugs during the study. Although men were allowed in the study, 85% of participants were female, with an average age of 44 years. Patients were randomized into 1 of 3 groups (1:1:1 ratio): one 16-mg naltrexone sustained-release (SR) plus 180 mg bupropion SR twice daily; one 8-mg naltrexone SR plus 180 mg bupropion SR twice daily; or placebo twice daily. The primary end points were percentage change in body weight and proportion of participants with a decrease in body weight of >5% at 1 year.
Results/Conclusions: After 1 year of therapy, patients in the placebo group lost, on average, 1.3% of their body weight, while the high-dose naltrexone group lost 6.1% and the low-dose group lost 5.0%. Almost one-half of the high-dose naltrexone group lost ≥5% of their baseline weight as did 39% of the low-dose group. These benefits were achieved at the cost of higher rates of nausea, headache, and constipation in both treatment groups, with nausea rates approaching 30% and headache and constipation approximately 15%.
Reviewer's Comments: This study shows moderate, but not trivial, benefit in a relatively young, low-risk population of predominantly women. The primary limitations of the study were the homogeneity of the study population and the high dropout rate; only 50% of participants made it to study completion. Not surprisingly, participants in the placebo arm were more likely to leave the study due to the inadequate weight loss, while participants in the medication arms tended to leave due to adverse effects. These balanced each other out in numbers, but inadequate follow-up is still concerning for the results. With that said, it is likely that at least in low-risk patients without active psychiatric illness or substance abuse, naltrexone combined with bupropion will help some people lose more weight than they would have with diet and exercise alone. (Reviewer-Christopher L. Knight, MD).

Keywords: Obesity, Weight Loss, Naltrexone, Bupropion

Print Tag: Refer to original journal article

Rimonabant for Weight Loss – Do Not Use It

Rimonabant for Prevention of Cardiovascular Events (CRESCENDO): A Randomised, Multicentre, Placebo-Controlled Trial.

Topol RJ, Bousser M-G, et al:

Lancet 2010; 376 (August 14): 517-523

Rimonabant, the THC-receptor antagonist, helps with weight loss has been taken off the market in Europe due to increased risk of suicide.

Background: Rimonabant is a new agent that blocks the endocannabinoid receptor, the same receptor that presumably mediates the intoxicating effects of marijuana or tetrahydrocannabinol (THC). Previous trials of rimonabant have shown reductions in waist circumference, body weight, and a variety of metabolic factors including triglycerides, glucose, and fasting insulin levels; however, it has also shown increased depression and anxiety.
Objective: To determine if rimonabant would improve major vascular event-free survival.
Design: Multicenter, randomized, placebo-controlled trial.
Participants: Participants included obese patients (defined as waist circumference >35 inches in women and >40 inches in men), age >55 years, and either documented cardiovascular disease or at least 2 risk factors. Exclusion criteria included prior bariatric surgery, obesity known to be secondary to an endocrine disorder, uncontrolled serious psychiatric illness, prior suicide attempt, or any medical disorder so severe the patient was not expected to survive for the 3-year study.
Methods: Patients were randomized to either rimonabant 20 mg or placebo. They were screened aggressively for neurological and psychiatric symptoms, starting at baseline, at 1 month, at 3 months, and then every 3 months for the remainder of the trial. The primary end point was a composite of cardiovascular death, myocardial infarction, or stroke. Patients were assessed at baseline, 30 days, 90 days, 180 days, and every 6 months thereafter for study end points and adverse effects. Patients were enrolled quickly, and a total of 18,695 patients were randomized.
Results/Conclusions: The trial was stopped in November 6, 2008, when regulatory agencies in Ireland, France, and Germany requested that all clinical research on rimonabant be stopped due to an excess risk of suicide in patients on the drug. This was based primarily on the results of earlier trials and on observations from open-label use for weight loss. However, similar findings were noted in the CRESCENDO trial, which had 4 suicides in the treatment arm compared to 1 suicide in the placebo arm as well as a nearly doubled rate of serious psychiatric effects.
Reviewer's Comments: The results of this trial are disappointing for the manufacturer, clinicians, and patients. Rimonabant initially appeared to have potential as a weight loss drug, but since its introduction in clinical trials, it has become apparent that the considerable risk of psychiatric adverse effects probably outweighs the benefit from weight loss. The sequence of events in this trial was particularly interesting, because the trial was not stopped by the investigators or by the independent monitoring board, but rather by governmental agencies in some countries in which the trial was conducted, based not on the outcomes of the trial but rather the adverse events seen in practice when rimonabant was used for weight loss. It appears that rimonabant is very unlikely to ever have meaningful therapeutic use, and will likely never be approved in the United States. (Reviewer-Christopher L. Knight, MD).

Keywords: Obesity, Rimonabant, Cardiovascular Events, Prevention

Print Tag: Refer to original journal article

Something New for Weight Loss?

Multicenter, Placebo-Controlled Trial of Lorcaserin in Weight Management.

Smith SR, Weissman NJ, et al:

N Engl J Med 2010; 363 (July 15): 245-256

Lorcaserin, a selective serotonin 2C agonist, is associated with more weight loss than placebo without evidence of valvular damage.

Background: Nonselective serotonin agonists modestly impact weight but have been implicated in valvular damage, possibly through serotonin 2B receptors. Lorcaserin is a selective serotonin 2C receptor agonist with potential to lower weight without an impact on valvular function.
Objective: To investigate the efficacy and safety of lorcaserin.
Design: Randomized, placebo-controlled, double-blind trial.
Participants: Patients aged 18 to 65 years, with a body mass index (BMI) of 30 to 45 or 27 to 45 and at least 1 cardiovascular risk factor, were eligible. Exclusion criteria included diabetes mellitus, depression, valvulopathy, and elevated blood pressure (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg).
Methods: Patients were randomized to either placebo or lorcaserin 10 mg twice daily for 1 year. At the end of the 1 year, patients on placebo continued it while patients on lorcaserin were randomized to either continuing the lorcaserin or placebo. The primary end points at 1 year were the proportion of patients achieving either a 5% or 10% decrease in body weight as well as absolute weight change. At year 2, the primary end point was a measure of weight loss maintenance. All patients received exercise and nutritional advice, and echocardiography was done every 6 months.
Results: 3812 patients were enrolled in the study; >80% were women, the average age was 44 years and the average body mass index (BMI) was 36. Approximately 50% of the original enrollees remained in the study at 1 year. At 1 year, patients receiving lorcaserin lost more weight than the placebo group (5.8 kg vs 2.2 kg). More patients on lorcaserin met weight loss goals (47.5% vs 20% for at least 5% of body weight and 23% vs 8% for at least 10%). At year 2, patients with at least 5% loss of weight on lorcaserin were more likely to maintain weight loss if they continued the lorcaserin (68% vs 50%). Multiple secondary end points were improved, including blood pressure, fasting glucose, and total cholesterol. The most common adverse events were headache and dizziness. There was no significant difference in valvular disease between treatment arms.
Conclusions: Lorcaserin, a serotonin agonist, was associated with more weight loss than placebo without evidence of valvular damage.
Reviewer's Comments: By mid-September, the Food and Drug Administration Advisory Committee will have met to discuss lorcaserin. If approved, it appears to have a reasonable safety profile at 2 years. Therefore, it may be a tool to jump-start a weight loss program for 1 to 2 years. However, similar to other weight loss agents, when the drug is stopped, weight starts to climb. In this trial, those on lorcaserin who were changed to placebo for the second year had weight gain and ended the 2-year trial with weight similar to those on 2 years of placebo. Therefore, behavioral change will continue to be the cornerstone of weight loss programs. (Reviewer-Mark E. Pasanen, MD).

Keywords: Lorcaserin, Obesity, Weight Management

Print Tag: Refer to original journal article

Spironolactone May Be Effective Alternative for HTN in Elderly

Spironolactone and Hydrochlorothiazide Decrease Vascular Stiffness and Blood Pressure in Geriatric Hypertension.

Kithas PA, Supiano MA:

J Am Geriatr Soc 2010; 58 (July): 1327-1332

Spironolactone and hydrochlorothiazide provide comparable blood pressure control in older healthy patients with mild essential hypertension.

Background: Hypertension (HTN) in the elderly is characterized by arterial stiffness, which in turn is associated with elevated aldosterone levels.
Objective: To test if spironolactone (SPIRO) is as effective as hydrochlorothiazide (HCTZ) in lowering blood pressure (BP) and arterial stiffness in older persons with HTN.
Design: Randomized double-blind trial.
Participants: 45 persons aged 60 to 79 years with essential HTN and otherwise in good health were included. Exclusion criteria were diabetes, creatinine >2.0 mg/dL, systolic blood pressure (SBP) >180 mm Hg, or the need for >1 antihypertensive drug.
Methods/Interventions: Subjects were randomized to initial doses of HCTZ 12.5 mg or SPIRO 25 mg. Doses were titrated over 2 months to a maximum dose of 50 mg of HCTZ or 100 mg of SPIRO to achieve a target SBP of <140 mm Hg. Study outcomes were changes in 24-hour ambulatory BP and measures of 2 measures of vascular stiffness: pulse pressure (PP; the difference between mean SBP and diastolic BP) and pulse wave velocity (PWV) determined by tonometry of carotid and femoral arteries.
Results: Subjects had a mean age of 70 years and a baseline blood pressure of 145/82. The mean study dose was 71 mg for SPIRO and 42 mg for HCTZ. Subjects on HCTZ required a mean potassium supplement dose of 23 mEg to maintain potassium level >3.5 mEq/L. SPIRO and HCTZ provided similar significant decreases in 24-hour ambulatory BPs over 6 months. SPIRO resulted in greater decreases in 24-hour SBP (16 vs 13 mm Hg) and nocturnal SBP (14 vs 10 mm Hg) than HCTZ. Measures of vascular stiffness, PP, and PWV were significantly and similarly lowered by SPIRO and HCTZ.
Conclusions: The authors concluded that SPIRO and HCTZ provide comparable reductions in BP and in measures of arterial stiffness in older persons with HTN.
Reviewer's Comments: Older studies indicate that SPIRO monotherapy is effective in treating essential HTN. Because geriatric HTN is associated with arterial stiffness and recent research indicates that local vascular production of aldosterone contributes to vascular stiffness and myocardial fibrosis, blockade of aldosterone receptors is a potentially attractive treatment target for geriatric HTN. This study suggests that SPIRO lowers SBP more effectively than HCTZ and that both agents provide qualitatively similar reductions in 24-hour BP and arterial stiffness measures. Study limitations include its very small size and that only healthy persons with very mild HTN manageable with monotherapy were enrolled. Further, the short study duration and exclusion criteria likely minimized potential complications of SPIRO, such as hyperkalemia and gynecomastia. Current guidelines recommend thiazide diuretics for most older persons with HTN, and this small study is dwarfed by the number of patients in the studies that support this recommendation. Still, there are patients in whom thiazides are contraindicated or less effective (eg, gout or creatinine clearance <30 cc/min), and it is worth knowing that SPIRO may be an effective alternative worth considering. (Reviewer-Jeff Wallace, MD, MPH).

Keywords: Hypertension, Older Adults, Monotherapy, Spironolactone, Hydrochlorothiazide

Print Tag: Refer to original journal article

New Higher-Strength Donepezil for AD Gains FDA Approval

Effectiveness and Tolerability of High-Dose (23 mg/d) Versus Standard-Dose (10 mg/d) Donepezil in Moderate to Severe Alzheimer's Disease: A 24-Week, Randomized, Double-Blind Study.

Farlow MR, Salloway S, et al:

Clin Ther 2010; 32 (July): 1234-1251

The new higher-strength donepezil product may be slightly more efficacious for the treatment of Alzheimer's disease but has more gastrointestinal side effects. It is also more expensive than the 10-mg dose that will soon be going generic.

Objective: To determine the efficacy and tolerability of increasing donepezil from 10 to 23 mg in persons with moderate-severe Alzheimer's disease (AD).
Design: Double-blind, randomized trial.
Participants: Persons aged 45 to 90 years with moderate-severe AD (Mini-Mental State Examination score, 0 to 20) on donepezil 10 mg for at least 12 weeks.
Methods: Subjects were randomized to receive a new sustained-release 23-mg donepezil product or to continue on standard 10-mg tablets over the 24-week study. Primary end points were changes in cognition, as measured by the Severe Impairment Battery (SIB), and in global function, as measured by the Clinician's Interview-Based Impression of Change Plus Caregiver Input Scale (CIBIC+).
Results: The mean age of the 1467 enrollees was 74 years; 62% were women, and 74% were white. The mean time on donepezil before study enrollment was approximately 2 years. After 24 weeks, the change in SIB score was significantly greater for subjects on 23 mg: +2.6 versus +0.4 ($P < 0.001$). Changes in the CIBIC+ score did not differ significantly between the 2 groups. Adverse treatment effects were significantly higher for persons on 23 mg: nausea, 11.8% versus 3.4%; vomiting, 9.2% versus 2.5%; diarrhea, 8.3% versus 5.3%; and weight loss, 4.7% versus 2.5%. Study discontinuation rates were 18% for the 23-mg dose group and 8% for those on 10 mg.
Conclusions: Increasing the donepezil dose from 10 to 23 mg is associated with cognitive benefits in patients with moderate-to severe AD.
Reviewer's Comments: When I first learned of a new donepezil product coming to market, the skeptic in me wondered if this might have anything to do with the donepezil 10-mg tablet patent expiring this upcoming November. On the other hand, there is physiologic rationale behind the new 23-mg sustained-release donepezil product that was developed to provide a higher daily-dose exposure to donepezil, in that the 10-mg donepezil dose inhibits cortical acetylcholinesterase activity by only 20% to 30%, suggesting that higher doses might confer additional effect and clinical benefit. In this study, the SIB measure of cognition did find a benefit associated with the higher dose of donepezil. The SIB is a 40-item instrument with a scoring range of 0 to 100, and the mean subject baseline SIB score in this study was 75. I question the clinical relevance of the 2-point advantage in the SIB score change that was found for the 23-mg dose group, especially as there were no significant differences detected in the CIBIC+ global function measure, which may better capture a clinically important change. Although this study showed a benefit in only 1 of the 2 primary end points and in neither of the 2 secondary end points, it was sufficient for the Food and Drug Administration to approve the new 23-mg dose, which your patients may soon be asking about and which should be available in the U.S. market by late summer. (Reviewer-Jeff Wallace, MD, MPH).

Keywords: Donepezil, Standard vs High Dose, Alzheimer's Disease

Print Tag: Refer to original journal article

Can Statins Prevent Dementia?

Age-Varying Association Between Statin Use and Incident Alzheimer's Disease.

Li G, Shofer JB, et al:

J Am Geriatr Soc 2010; 58 (July): 1311-1317

The use of statins before, but not after, age 80 years may decrease the risk of Alzheimer's disease.

Background: Data regarding the effect of statins on the incidence of Alzheimer's disease (AD) is mixed. Exploratory studies indicate that statins started in relatively early old age reduce AD onset more than treatment initiated later, and that statins may be more beneficial in reducing AD for persons carrying the apolipoprotein E (APOE) ε4 allele, a known genetic risk factor for AD.
Objective: To determine if the effects of statins on AD incidence vary by age of treatment onset or by the presence of APOE ε4 allele.
Design/Participants: Prospective observational study involving 3392 community-dwelling members of a health maintenance organization (HMO) who were age ≥65 without dementia.
Methods: Subjects were assessed biennially for AD. Statin exposure was determined from the HMO pharmacy database. Proportional hazards models were used to explore the association between statins and AD and potential modifying effects of age and APOE ε4 allele status.
Results: Baseline subject mean age was 75 years; 25% carried an APOE ε4 allele, and 23% had taken statins for an average of 5.4 years. Eight percent of subjects developed AD over 6.1 years of follow-up. Statin use was associated with a decreased risk of AD (HR, 0.62; 95% CI, 0.40 to 0.97) after adjusting for demographics and cardiovascular risk factors. This association differed by age with a hazard ratio of 0.44 (95% CI, 0.25 to 0.78) observed among those aged <80 years versus 1.22 (95% CI, 0.61 to 2.42) for subjects aged ≥80 years. No significant association was found between AD and the use of lipid-lowering agents other than statins. Although the effect of statin use by APOE ε4 allele status was not significant, the effect of statins on lowering risk of AD was greatest among those with an ε4 allele.
Conclusions: Statin use in early old age, but not in late age, may prevent or delay the onset of AD.
Reviewer's Comments: The main study findings (that statin use is associated with a roughly 40% reduction in risk of developing AD, and that this risk reduction is diminished with advancing age) are consistent with previous studies. The loss of benefit for persons aged ≥80 years may be due to a survival effect, such that persons who live to a very old age and do not have dementia may have different characteristics that protect them from developing dementia with or without statin use. Alternatively, there may be a window of opportunity for statins to protect against AD that needs to be relatively early in the neuropathologic course of AD. Only a randomized, controlled trial can definitively answer questions about the potential beneficial effect of statins on AD incidence. As such a trial will entail large numbers of patients followed for prolonged periods, we are still many years from determining how these findings should be translated into clinical practice, if at all. (Reviewer-Jeff Wallace, MD, MPH).

Keywords: Alzheimer's Disease, Statins, Apolipoprotein E, Age

Print Tag: Refer to original journal article

CAM Is Preferred Bedside Tool for Delirium Screening

Does This Patient Have Delirium? Value of Bedside Instruments.

Wong CL, Holroyd-Leduc J, et al:

JAMA 2010; 304 (August 18): 779-786

The Confusion Assessment Method is the preferred tool for delirium screening due to its accuracy, brevity, and ease of use by clinical and lay interviewers.

Background: Research suggests that health care providers do a poor job at diagnosing delirium.
Objective: To determine the diagnostic accuracy of bedside delirium instruments.
Design/Methods: MEDLINE and EMBASE were searched through May 2010 for delirium diagnostic studies. Studies had to use the *Diagnostic and Statistical Manual of Mental Disorders III*, *III-R*, or *IV* as a reference standard, have a specialist physician (eg, geriatrician, neurologist, or psychiatrist) perform patient evaluations using the reference standard, and have participants with and without delirium. The clinical tool tested for delirium diagnosis in each study had to be clinically feasible without the use of special equipment and had to able to be performed by a non-expert. Studies assessing children or alcohol-related delirium were excluded.
Results: 25 articles met inclusion criteria and assessed 11 different bedside instruments with a total of 3027 participants. The prevalence of delirium was 9% to 63% depending on the practice site. The Global Attentiveness Rating (GAR), Memorial Delirium Assessment Scale (MDAS), Confusion Assessment Method (CAM), Delirium Rating Scale Revised-98 (DRS-R-98), Clinical Assessment of Confusion (CAC), and Delirium Observation Screening Scale (DOSS) all had positive likelihood ratios (LRs) of >5.0 (ie, positive screen increased pretest probability of delirium by ≥30%). The Mini-Mental State Examination (MMSE) was the least helpful tool for identifying delirium (positive LR of 1.6 for a score <24/30). The negative LR for the GAR, MDAS, CAM, DRS, DRS-R-98, DOSS, Nursing Delirium Screening Scale, and MMSE was <0.2 (ie, negative/normal test decreased pre-test probability of delirium by ≥30%). Overall, CAM, which takes ≤5 minutes to perform, had the most favorable profile (positive LR of 19; negative LR of 0.19) of the tools tested in >1 study. GAR, which can be performed in 2 minutes, performed better (positive LR of 65; negative LR of 0.06), but has been studied only once and only with geriatricians.
Conclusions: CAM is the preferred method for delirium screening due to its accuracy and ease of use by clinical and lay interviewers. It currently is the most widely used assessment tool for delirium.
Reviewer's Comments: When I am screening for delirium, I agree with the authors and use CAM. CAM first requires the use of tools such as the Digit Span Test and/or Modified Mini-Cog (ie, orientation, clock-drawing, recall of 3 objects) to assess cognitive function and engage the patient. After assessing the patient in this manner, the examiner uses the CAM questions. Is there an acute change in mental status with a fluctuating course? Does the patient have trouble focusing attention? Is the patient's speech disorganized or incoherent? Is the patient's level of consciousness anything other than alert? For CAM to be positive, the answers to the first 2 questions and one of the last 2 questions must be yes. Modifications to CAM exist for evaluating persons in the emergency department, ICU, and nursing home. Information on how to use CAM is available online. (Reviewer-Melissa Hagman, MD).

Keywords: Delirium, Screening, Confusion Assessment Method, Global Attentiveness Rating, MMSE

Print Tag: Refer to original journal article

Middle-Aged and Older Men Who Use ED Drugs Have Increased Risk of STD

Sexually Transmitted Diseases Among Users of Erectile Dysfunction Drugs: Analysis of Claims Data.

Jena AB, Goldman DP, et al:

Ann Intern Med 2010; 153 (July 6): 1-7

When prescribing erectile dysfunction drugs, providers should counsel patients regarding safe sexual practice and screen for sexually transmitted diseases.

Background: Erectile dysfunction (ED) drugs have become widely used, but we have little understanding of the relationship between the use of ED drugs and the risk of sexually transmitted diseases (STDs).
Objective: To determine STD rates among users and non-users of ED drugs.
Design: Retrospective cohort study.
Methods: An analysis of an insurance claims database including 1,410,806 men aged >40 years with employer-based health insurance from 44 companies during a study period from 1997 to 2006. Pharmacy claims and diagnostic codes were reviewed to determine STD prevalence among users and non-users of ED drugs in the year before and the year after receiving an ED drug prescription.
Results: ED drug users were older (61 vs 59 years) and had more co-morbid chronic medical conditions than non-users of ED drugs. In the year before starting ED drugs, ED drug users had higher rates of STDs than non-users (214 vs 106 annually per 100,000 men; *P* =0.003), and the prevalence of STDs remained higher among ED drug users in the year after starting ED drugs (105 vs 65; *P* =0.004). Initiating ED drug treatment had no significant effect on the rate of STDs.
Conclusions: Men who use drugs for ED have an increased rate of STDs. "Counseling about safe sexual practices and screening for STDs should accompany the prescription of ED drugs."
Reviewer's Comments: This observational study suggests that men concerned about sexual performance may practice more unsafe sex. The authors cite data indicating that middle-aged and older men use condoms less frequently than younger men, perhaps due in part to a decreased need for contraception. They also review a survey of primary care providers that showed providers rarely or never discussed sexual risk factor reduction with middle-aged or older men. Prescribing an ED drug provides an opportunity to assess STD risk, advise patients regarding safe sexual practices, and screen for STDs. (Reviewer-John V.L. Sheffield, MD).

Keywords: Erectile Dysfunction, Treatment, Sexually Transmitted Diseases

Print Tag: Refer to original journal article

International AIDS Society-USA Panel Issues New Treatment Recommendations

Antiretroviral Treatment of Adult HIV Infection: 2010 Recommendations of the International AIDS Society–USA Panel.

Thompson MA, Aberg JA, et al:

JAMA 2010; 304 (July 21): 321-333

Antiretroviral treatment of HIV infection is recommended for asymptomatic patients with CD4 cell counts ≤500/μL.

Background: Emerging data regarding the adverse effects of untreated chronic HIV infection and the growing number of new treatment options made the International AIDS Society-USA Panel feel the time was right to revise its recommendations for antiretroviral treatment of adult HIV infection.
Objective: To provide updated management recommendations for treating adults infected with HIV in the developed world. In particular, the panel sought to advise providers on when to initiate antiretroviral treatment, first-line treatment options, monitoring, when to change a treatment regimen, and appropriate secondary treatment options.
Methods: The expert panel reviewed data published or presented at scientific conferences since its last report in 2008. They performed a PubMed search, reviewed scientific conference abstracts, and requested updated treatment and adverse event data from drug manufacturers. Recommendations were based on a consensus of the entire panel. **Results/Conclusions: (*Main Recommendations)*** Patient readiness for antiretroviral therapy should be assessed before initiating antiretroviral treatment. Antiretroviral therapy is recommended for asymptomatic patients with a CD4 cell count ≤500/μL and for all patients with HIV-related symptoms. Treatment is also recommended for patients, regardless of the CD4 count, with specific medical conditions including pregnancy, HIV RNA >100 000 copies/mL, rapidly declining CD4 count (>100 cells/μL per year), active hepatitis B or C, active cardiovascular disease, or HIV-associated nephropathy. Antiretroviral therapy should also be considered for asymptomatic patients with a CD4 count >500/μL. Preferred components of the initial treatment regimen include tenofovir/emtricitabine or abacavir/lamivudine in combination with efavirenz, ritonavir-boosted atazanavir (atazanavir/r), darunavir/r, or raltegravir. The goal of treatment is to suppress HIV RNA below the threshold of detection. Patients on treatment require frequent monitoring to detect and manage treatment failure early.
Reviewer's Comments: The pendulum has swung back toward early treatment of chronic HIV infection. HAART is now strongly recommended for all patients with a CD4 cell count ≤500/μL and should also be considered for patients with a CD4 count >500/μL. The rationale for earlier treatment is that antiretroviral therapy restores immune function and improves survival. Potent regimens with a decreased pill burden and lower toxicity are now available, and studies indicate that patients treated earlier may be less susceptible to drug toxicity. In addition, there is growing concern that the chronic inflammatory state associated with untreated HIV infection may contribute to end-organ damage, irreversible immune destruction, and mortality. (Reviewer-John V.L. Sheffield, MD).

Keywords: HIV, Antiretroviral Treatment

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Colchicine for Acute Gouty Arthritis -- Low vs High Dose

High Versus Low Dosing of Oral Colchicine for Early Acute Gout Flare: Twenty-Four–Hour Outcome of the First Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Comparison Colchicine Study.

Terkeltaub RA, Furst DE, et al:

Arthritis Rheum 2010; 62 (April): 1060-1068

Low-dose colchicine is as effective as higher-dose colchicine in relieving pain associated with acute gout flares. Higher-dose colchicine is associated with significant and severe gastrointestinal toxicity.

Background: Colchicine is commonly used for the treatment of acute gout flares. Only one well-designed trial has been published, however; this study used high doses of colchicine, and gastrointestinal side effects were common.
Objective: To evaluate a standard high-dose versus low-dose colchicine regimen compared to placebo for the treatment of acute gout flares.
Participants/Methods: This was a multicenter, randomized, double-blind, placebo-controlled trial. Eligible patients had confirmed gout and at least 2 gout flares in the previous year. A total of 575 patients were randomized to 1 of 3 groups: (1) high-dose colchicine (1.2 mg followed by 0.6 mg hourly for 6 hours); (2) low-dose colchicine (1.2 mg followed by 0.6 mg 1 hour later, followed by 5 hourly placebo pills); or (3) placebo (2 placebo pills, followed by 6 hourly placebo pills). All subjects received a blinded pack of study medication and were instructed to contact a 24-hour study call center at the onset of a gout flare; patients then self-administered the medications until they were completely gone or until severe adverse effects occurred. The principal end point was a 50% relief of pre-treatment pain within the first 24 hours without the need for rescue medications such as non-steroidal anti-inflammatory drugs (NSAIDs) or prednisone.
Results: Of the 575 eligible subjects, 185 had acute gout flares and took their study medication: 52 took high-dose colchicine, 74 received low-dose colchicine, and 59 received placebo. Both colchicine protocols were significantly superior to placebo in terms of the primary outcome (≥50% relief of pain within the first 24 hours): 32.7% of the high-dose group, 37.8% of the low-dose group, and 15.5% of the placebo group responded. Rescue medications (mostly NSAIDs) were taken by 34.6% of the high-dose group, 31.1% of the low-dose group, and 50% of the placebo group. Adverse events, mostly gastrointestinal, were reported by 36.5% of the low-dose group, 76.9% of the high-dose group, and 27.1% of the placebo group (significantly more adverse effects occurred in the high-dose group). All of the adverse effects in the low-dose and placebo groups were mild or moderate in intensity; 19.2% of patients in the high-dose group reported severe diarrhea.
Conclusions: Low-dose colchicine was more effective than placebo at reducing acute gout pain within 24 hours and was as effective as high-dose colchicine. High-dose colchicine was associated with significantly more gastrointestinal toxicity, much of it severe.
Reviewer's Comments: This study offers persuasive evidence that a low-dose regimen of colchicine (1.2 mg followed by 0.6 mg 1 hour later) provides significant relief from the pain associated with acute gout. The low-dose colchicine regimen was well tolerated, with adverse events not significantly different from placebo. (Reviewer-Paul R. Sutton, PhD, MD).

Keywords: Gout Colchicine, Medication-Associated Adverse Effects

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Consider Tai Chi to Reduce Fibromyalgia Symptoms

A Randomized Trial of Tai Chi for Fibromyalgia.

Wang C, Schmid CH, et al:

N Engl J Med 2010; 363 (August 19): 743-754

Twelve weeks of tai chi classes and home practice can significantly improve many symptoms of fibromyalgia and overall function.

Background: Fibromyalgia is a common clinical condition that is difficult to treat. Patients report fatigue and widespread musculoskeletal pain, which limits activities and responds poorly to medications. Tai chi is a defensive Chinese martial art and is a form of meditation. The practitioner focuses on slow body movements. Preliminary studies suggest that tai chi may improve the quality of life in patients with fibromyalgia.
Objective: To assess the symptomatic response to tai chi versus control in patients with fibromyalgia.
Design: Single-blind, randomized, controlled trial.
Participants/Methods: Patients at least 21 years of age who met the diagnostic criteria for fibromyalgia were eligible. There were many exclusion criteria, resulting in a relatively healthy patient population. Participants were randomized to 12 weeks of tai chi or wellness education and a stretching routine. Tai chi sessions occurred twice a week for 60 minutes, and participants were encouraged to practice at home for at least 20 minutes. Wellness education and stretching also occurred for an hour twice a week, with 20 minutes of daily home stretching recommended. The main outcome was a change in the 100-point Fibromyalgia Impact Questionnaire (FIQ) from baseline to repeat measurements at 12 weeks. A clinically meaningful change was a decline of 8.1 points. Secondary end points included changes in pain, sleep, exercise, tenderness, 6-minute walk test, depression, and quality-of-life measures. Testing was also repeated at 24 weeks.
Results: 66 participants were randomized. The average age was 50 years, 86% of subjects were women, and the average duration of disease was 11 years. The tai chi group had significant improvement in all measures. Initial mean FIQ scores were in the 60s at baseline for each group and declined by an average of 27.8 in the tai chi group and 9.4 in the control group; 79% in the tai chi group achieved clinically meaningful improvement at 12 weeks compared to 39% in the control group. These benefits persisted in the 24-week testing. The tai chi group also had significantly more improvement in measures of sleep, global functioning, depression, 6-minute walk test, and the Medical Outcomes Study 36-Item Short-Form Health Survey physical and mental component scores. No adverse events were noted.
Conclusions: A 12-week tai chi program is safe and effective in reducing symptoms and improving quality of life in patients with fibromyalgia.
Reviewer's Comments: This relatively short intervention showed significant improvement in many of the symptoms of fibromyalgia in patients with chronic symptoms. Participants volunteered for the study, and the intervention was free. If patients can overcome the cost and motivation hurdles, tai chi seems to be a low-risk excellent option as part of the treatment for fibromyalgia. (Reviewer-Deborah L. Greenberg, MD).

Keywords: Fibromyalgia, Tai Chi

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Boceprevir Improves Outcomes in Treating Genotype 1 Hepatitis C

Efficacy of Boceprevir, an NS3 Protease Inhibitor, in Combination With Peginterferon Alfa-2b and Ribavirin in Treatment-Naive Patients With Genotype 1 Hepatitis C Infection (SPRINT-1): An Open-Label, Randomised, Multicentre Phase 2 Trial.

Kwo PY, Lawitz EJ, et al:

Lancet 2010; 376 (August 28): 705-716

Adding boceprevir to interferon and ribavirin can double the sustained virologic response rates when treating genotype 1 hepatitis C.

Background: Hepatitis C is difficult to treat, requiring 6 to 12 months of peginterferon and ribavirin, each of which has problematic side effects. For certain hepatitis C genotypes, particularly genotype 1, even the most effective combination succeeds only 40% to 50% of the time.
Design: Randomized, open-label, therapeutic trial.
Participants: 595 treatment-naïve patients with genotype 1 hepatitis C were studied. Patients with significant anemia, thrombocytopenia, neutropenia, decompensated cirrhosis, HIV disease, or pre-existing psychiatric disease were excluded.
Methods: There were 5 treatment groups. One group received peginterferon and ribavirin for 48 weeks. The 4 intervention groups were divided in a 2-by-2 fashion. Two groups received 48 weeks of treatment, and 2 groups received 28 weeks of treatment. The other randomization was to use a lead-in of 4 weeks of peginterferon and ribavirin and then start boceprevir, or to start boceprevir at the beginning of treatment. Patients in all groups were followed up for 24 weeks after completing therapy to assess for a sustained virologic response.
Results/Conclusions: All 4 boceprevir groups had significantly better sustained virologic responses than the control group. The most striking differences were in a group treated for 48 weeks with a 4-week boceprevir-free lead-in period, in which the sustained response rate was 75% compared to 38% in the control group. Patients in the boceprevir groups also had a much quicker suppression of hepatitis C virus, with virologic responses approaching 60% to 70% after 8 weeks of therapy compared to 20% to 30% in the control group. Patients with a more rapid virologic response were much more likely to achieve sustained response than those with slow responses, and those who had >1.5 log reduction in viral load after 4 weeks seemed to do well with 28 weeks of therapy, whereas patients with less reduction did better with 48 weeks of therapy with boceprevir.
Reviewer's Comments: This is a phase 2 trial, so it will be a while before this drug is ready for market. There were also major flaws in the design. It was open label, and it was underpowered to detect important differences between treatment groups. However, the results of the trial certainly suggest that there is a benefit to adding boceprevir to treatment with peginterferon and ribavirin. However, despite these limitations, this still represents a significant step forward in the treatment of a tenacious, problematic disease. (Reviewer-Christopher L. Knight, MD).

Keywords: Hepatitis C, Boceprevir, Peginterferon Alfa-2B, Ribavirin

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Risk From Childhood Cancer Continues Into Adulthood

Long-Term Cause-Specific Mortality Among Survivors of Childhood Cancer.

Reulen RC, Winter DL, et al:

JAMA 2010; 304 (July 14): 172-179

Adults with a history of childhood cancer are at higher risk of dying from variety of causes compared to the general population, especially second primary cancers.

Background: As treatment for childhood cancer advances, more patients are surviving into adulthood. Their risk for long-term complications of the original cancer and its treatment are higher than that of the general population. Large studies of this patient population have been lacking.
Objective/Design: To characterize the long-term, disease-specific mortality of childhood cancer survivors in a large population-based cohort.
Methods: The British Childhood Cancer Survivor Study follows 17,981 subjects who were 5-year survivors of childhood cancer and who were diagnosed between 1940 and 1991. All deaths were obtained through the National Health Service Central Registers, and the cause of death was verified through a review of death certificates. The primary outcome was the standardized mortality ratio (SMR) and absolute excess risk (AER) for each cause of death. The SMR is the number of observed deaths divided by the expected deaths for the general population. The AER is the number of deaths beyond those expected per 10,000 patient-years.
Results: 3049 (17%) initial 5-year survivors died during an average follow-up of 25.6 years from the time of diagnosis. The SMR for all-cause mortality was 10.7 or >10 times the expected death rate compared to the general population. Excluding recurrence of the original cancer, the SMR was 3.9. The risk of death was higher in almost all disease categories except mental health and suicide. The highest risks were from genitourinary disease, respiratory disease, infections, and second primary cancer. Excess mortality beyond 45 years from the time of diagnosis was due largely to cardiac disease and second primary cancers.
Conclusions: The risk of excess mortality from childhood cancers continues beyond 25 years from the time of original diagnosis. Most of the excess risk in these long-term survivors is due to treatment of the original disease, particularly cardiovascular disease and second primary cancers.
Reviewer's Comments: In the practice of internal medicine, we often see a patient with a distant history of leukemia or other childhood cancer who is living a seemingly normal life, and we treat them clinically the same as our general patient population. This study points out that these patients are at a higher risk for many chronic medical conditions and for second cancers. Perhaps we should be paying closer attention to modifiable risk factors and cancer screening in this patient population. (Reviewer-Deborah L. Greenberg, MD).

Keywords: Childhood Cancer, Long-Term Risks, Adulthood

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Medication Errors Common at Hospital Admission

Results of the Medications At Transitions and Clinical Handoffs (MATCH) Study: An Analysis of Medication Reconciliation Errors and Risk Factors at Hospital Admission.

Gleason KM, McDaniel MR, et al:

J Gen Intern Med 2010; 25 (May): 441-447

Medication errors are common at hospital admission. Errors of sufficient importance to require additional physician orders occurred in more than one-third of admissions in this study. Older patients and those with multiple medications are at greatest risk.

Background: Medication errors at transitions of care are a common source of potentially harmful events. The Joint Commission made medication reconciliation a National Patient Safety Goal in 2005.
Objective: To understand the frequency and risk factors for potentially harmful medication errors at a hospital admission.
Design: This study involved a single institution from a large academic medical center.
Participants/Methods: Study pharmacists approached all patients admitted to the medicine service over a 14-month period in 2006 to 2007. Participants were interviewed by the study pharmacists to reconcile the medication history obtained by the admitting physician with the patient's current outpatient medication regimen. Sources of information included patients, family members, caregivers, online documentation, prescription bottle labels, self-prepared medication lists, and community pharmacies. The authors defined medication errors as differences between medications prescribed at admission and the pharmacist-reconciled medication list that required order changes. Medications errors were classified using a well-established national system according to potential harm: (1) no potential harm; (2) increased monitoring or intervention to preclude harm; or (3) potentially harmful.
Results: A total of 651 patients participated. Pharmacists spent an average of 21.2 minutes interviewing patients. The pharmacists identified 309 medication errors resulting in physician order changes; these errors were identified in 234 of 651 study patients (35.9%). Of these, 198 (64%) had the potential to cause harm or require additional monitoring or intervention. In multivariate analysis, risk factors associated with errors that might require additional monitoring or cause harm were age ≥65 years (OR, 2.17; 95% CI, 1.09 to 4.30) and increased number of medications on admission (OR, 1.21; 95% CI, 1.14 to 1.29). Presenting a medication list on admission was protective against potentially harmful medication errors (OR, 0.35; 95% CI, 0.19 to 0.63).
Conclusions: Medication errors that required a new physician order occurred in 35.9% of admissions to a large urban academic medical center. The majority of these errors had the potential to cause harm or require additional intervention.
Reviewer's Comments: This was a large and methodologically well-done study, although it was from a single institution. The high fidelity reconciliation process in this study was time consuming; a trained pharmacist spent >20 minutes interviewing a patient and reviewing other medication records after the house staff physicians obtained a primary medication history. Although all patients were at risk for medication errors, older age and more admission medications were risk factors for errors. This may help us identify patients for whom we should expend additional resources to ensure an accurate medical history. Finally, it is intriguing that a patient-provided medication list was significantly protective against medication errors, perhaps pointing to something that can be done in primary care to prevent medication errors at hospital admission. (Reviewer-Paul R. Sutton, PhD, MD).

Keywords: Medication Reconciliation, Medication Errors, Hospital Medicine

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Fatal Medication Events in Hospitals -- Does Time of Year Make a Difference?

A July Spike in Fatal Medication Errors: A Possible Effect of New Medical Residents.

Phillips DP, Barker GEC:

J Gen Intern Med 2010; 25 (August): 774-779

Using a national dataset of death certificates between 1979 and 2006, this study found an increase in fatal medication errors in July. This "July Effect" was most pronounced in regions with the highest concentration of teaching hospitals.

Background: Each July brings an influx of inexperienced new residents and fellows to training programs across the United States. It remains uncertain whether their inexperience results in an increase in medical errors or harm to patients. A number of previous studies have not identified a so-called "July Effect," although one recent study found more unsafe or potentially unsafe events at the beginning of the academic year in an Australian anesthesia training program.
Objective: To determine if fatal medication errors would be increased during July as a result of the influx of new medical trainees.
Methods: The authors utilized a very large dataset of U.S. death certificates spanning the years 1979 to 2006 (n=62,338,584). Fatal medication errors were defined by death certificates with "medication error" listed as the primary cause of death. These fatal medication errors were thought to be potentially preventable. The authors calculated the expected number of fatal medication errors each month by a least squares regression estimate. The July Effect was calculated as the ratio of observed-to-expected fatal medication errors in July compared with other months of the year. Although the authors could not determine whether deaths occurred in a teaching hospital, they did know the county in which the death occurred and calculated the July Effect in counties with teaching hospitals compared to counties without teaching hospitals.
Results: Fatal medication errors occurred more often in July than in other months of the year in 21 of 28 years in the death certificate dataset. Overall, the July Effect, or ratio of observed fatal medication errors compared to expected fatal medication errors, was 1.062 (95% CI, 1.023 to 1.100). The ratio of observed-to-expected fatal medication errors significantly exceeded 1 only during the month of July. The July Effect was observed only for deaths in the hospital and was not seen in deaths occurring before hospital arrival. All-cause mortality, surgical errors, and adverse effects as a whole were not increased during July. The July Effect was significant only in counties with teaching hospitals; regions with a greater concentration of teaching hospitals displayed a July Effect of greater magnitude.
Conclusions: Fatal medication errors in hospitals increased in July. This increase was most pronounced in regions with more teaching hospitals.
Reviewer's Comments: This is likely to be a highly controversial paper. Fatal medication errors may be more common in teaching institutions in July, at the beginning of the academic year when trainees are at their least experienced. Although causality cannot be inferred from this kind of study, there is already considerable momentum toward increasing supervision of medical trainees. Even accepting the conclusion of this paper, it is not clear how best to reduce fatal medication errors in teaching hospitals. (Reviewer-Paul R. Sutton, PhD, MD).

Keywords: Fatal Medication Errors, Academic Medical Centers, Medical Education

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Do Not Count on Pharmacy CMI to Educate Patients on Medications

Evaluation of Consumer Medication Information Dispensed in Retail Pharmacies.

Winterstein AG, Linden S, et al:

Arch Intern Med 2010; 170 (August 9): 1317-1324

The medication information dispensed at retail pharmacies is often suboptimal in terms of content, readability, or both.

Background: Pharmacies are required by law to provide "useful" consumer medication information (CMI) when a new medication is dispensed. Although the law specifically prohibits the Food and Drug Administration (FDA) from specifying or regulating this information, the agency has developed guidelines for CMI. Most pharmacies provide leaflets developed by commercial vendors, which vary in terms of content and readability.
Objective: To assess the utility of consumer medication information for lisinopril and metformin dispensed at retail pharmacies across the country.
Methods: For each drug, a panel made up of an endocrinologist, an internist, a pharmacologist, and a community pharmacist developed CMI “usefulness criteria,” based on FDA guidelines for clinical content (including indications, contraindications, precautions, adverse effects and what to do, accuracy, and comprehensibility.) Trained professional shoppers filled prescriptions for lisinopril and metformin at a random sample of 365 retail pharmacies across the country. At 94% of pharmacies, the “patients” received CMI with their prescriptions. This CMI was judged against the usefulness criteria.
Results: Leaflets ranged in length, from 33 to >2000 words. Three percent of lisinopril CMI and 0.3% of metformin CMI were judged to meet >80% of the usefulness criteria. The lisinopril CMI met a mean of 60% of the criteria, and the metformin CMI met a mean of 57% of the criteria. Huge variability was seen in content, conciseness, and presentation/readability. Less than one-third used a font size of ≥10, and only 7% bulleted key points. More than 90% were written at an eighth grade or higher reading level. Although white space around content is supposed to enhance readability, available space on most leaflets was filled with ads, coupons, quotes, or general information about the disease state.
Conclusions: The content, excessive length, format, and reading level of CMI dispensed in retail pharmacies are disconcerting.
Reviewer's Comments: Do not count on pharmacy-dispensed CMI to educate your patients about new medications. Although the information is being handed out almost all the time (the good news), the chosen content, the reading level, and the format limit the utility of most of these leaflets. I do not think I have ever actually read one of mine, have you? (Reviewer-Karen A. McDonough, MD).

Keywords: Patient Education, Consumer Product Information, Pharmacies

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