For treatment of polymyalgia rheumatica, start with 15 mg/day of prednisone and taper very slowly to maintain remission, decreasing no more than 1 mg/day every 2 months. This approach limits total dose of prednisone by reducing relapse rates and minimizing steroid side effects.

**Background:** Polymyalgia rheumatica (PMR) is exquisitely responsive to prednisone, and initial treatment response is gratifying. However, most of us have experienced frustration with this disorder as we attempt to prevent relapse and avoid higher doses of prednisone that are often needed to control symptoms over the long run.

**Objective:** To examine peer-reviewed literature on steroid treatment schedules and doses as well as effective use of steroid-sparing agents.

**Design:** Systematic review of 30 published series of PMR patients (13 randomized trials and 17 observational studies).

**Methods:** Of the initial 2220 patients with PMR included in these studies, 153 (6.9%) were diagnosed with giant cell arteritis (GCA) at onset or subsequently, and were excluded from further study. A total of 2161 patients were included in the final analysis. Also included in this review were 5 trials of methotrexate, 1 each of azathioprine and infliximab, and 3 studies of NSAIDs, all used as steroid-sparing agents in PMR.

**Conclusions:** Initial treatment with prednisone 15 mg/day is most likely to produce remission in 99% of patients, and it seems to be as effective as higher doses when used for initial treatment. Starting with prednisone <11 mg/day allowed 30% of treated patients to relapse, whereas only 70% were able to discontinue therapy after 4 years. The initial dose of prednisone needed to produce remission (15 mg/day) should ideally be followed by gradual tapering to a maintenance dose of 10 mg/day, followed by a very slow tapering schedule of decreasing <1 mg/day approximately every 2 months. Remission is defined by an absence of clinical symptoms and normal range sedimentation rate. Overall, the total duration of PMR is thought to be in the range of 2 to 4 years with a fairly high overall rate of relapse in this time period. Approximately 50% of patients overall were able to discontinue prednisone after 2 years of therapy; however, fewer patients started on <10 mg/day prednisone were able to discontinue prednisone therapy at 4 years (70% vs 82% on 10 to 20 mg/day dose). Steroid side effects are minimized by using the lowest effective dose.

**Reviewer's Comments:** This study has several flaws: lack of agreement on treatment protocols, PMR definition criteria, and outcome criteria in these reviewed articles seriously hamper the ability to draw meaningful conclusions from different datasets. The small number of articles on steroid-sparing agents also limits the ability to draw conclusions in this area, and the authors did not recommend starting any steroid-sparing agent in their summary algorithm of PMR treatment. However, it is helpful to know that their review identified a common starting prednisone dose (15 mg/day) that did correlate with a lower relapse rate and thus lower total steroid dose over the 2- to 4-year treatment period. (Reviewer-Peggy Schlesinger, MD).
In patellofemoral pain syndrome, 6 weeks of supervised physical therapy followed by a home exercise program helps improve outcomes with less pain and better function.

**Background:** Patellofemoral pain syndrome (PPS) affects up to 50% of teenage girls and often extends throughout adulthood; 25% of new running injuries seen by sports medicine practices in the Netherlands were classified as PPS. No clear pathology underlies this chronic knee pain problem that can and does impair function over time. Typically, patients complain of knee pain around the patella when weight bearing on a bent knee. Activities such as going up or down stairs, squatting, using a clutch in a car, getting up after prolonged sitting (in a movie theater for instance) can elicit knee pain in affected patients. Quadriceps strengthening and orthotics have been advocated as treatment for this common condition, along with taping or bracing the knee. "Usual care" in this article refers to limiting activities that cause pain, and resting if pain occurs. There is a paucity of well-controlled clinical trials evaluating the effectiveness of intervention with therapeutic exercise on pain and resultant disability in this group of patients.

**Objective:** To compare the effectiveness of supervised exercise therapy with that of usual care for PPS.

**Participants/Methods:** 131 patients aged 14 to 40 years with knee pain for 2 to 24 months and confirmatory clinical findings were diagnosed with PPS and were randomized into 2 groups: 66 patients received usual care, and 65 received a 6-week program of supervised physical therapy exercising followed by a 3-month program of home exercises designed to improve lower extremity muscle strength. All patients received instruction in isometric quadriceps strengthening exercises they were to do daily at home. Primary outcomes were self-reported recovery, pain at rest, and pain with activity, as well as overall function at 3 and 12 months.

**Results:** Outcomes in the exercise arm of this study produced significantly less pain at 3 months and 12 months both at rest and with activity. There was significant improvement in function at 3 months in the intervention group, and at 12 months, there was improved function compared to baseline in both groups. Differences in self-reported recovery at 12 months were not statistically significant between groups. Use of both NSAIDs and topical therapies for pain was significantly higher in the control group.

**Reviewer's Comments:** This study supports use of a supervised strengthening program for PPS over 3 months, with an ongoing home exercise program for 12 months following diagnosis. Significant reduction in knee pain at rest and with exercise, reduction in NSAID use, topical treatments, and bracing resulted from this intervention. Exercise, although initially difficult, can reduce pain in this common condition. (Reviewer-Peggy Schlesinger, MD).

© 2010, Oakstone Medical Publishing

Keywords: Patellofemoral Pain Syndrome, Knee Pain, Supervised Exercise

Print Tag: Refer to original journal article
Three or more positive tests of shoulder function can rule in subacromial impingement syndrome, while <3 positive tests can rule it out.

**Background:** Certain tests for shoulder motion produce pain in patients with subacromial impingement syndrome (SAIS). Performing these particular maneuvers, either individually or in combination, can confirm or rule out SAIS.

**Objective:** To determine the best test or combination of tests that can produce diagnostic accuracy in SAIS. This is a useful inquiry, as the diagnosis needs to be standardized and optimized to study further which therapies offer the most benefit.

**Design:** Prospective, blinded cohort study.

**Participants:** 55 consecutive patients presenting to orthopedist's office with shoulder pain as the primary complaint lasting at least 1 week were included in this study. There were 47 men and 8 women, with an average age of 40.6 years and symptom duration from 2 to 230 months.

**Results:** The gold standard for diagnostic accuracy in SAIS was arthroscopy; however, patients were not removed from study if they had concomitant rotator cuff tears or other shoulder pathology discovered at arthroscopy. In fact, 15 of 16 patients who were diagnosed with SAIS at surgery also had other significant shoulder pathology, most commonly labral tear. Only 1 patient had SAIS as the only finding during surgery. Of 55 patients, 39 (71%) had no evidence of SAIS at surgery. There were 5 clinical maneuvers investigated to determine their usefulness in diagnosing SAIS: (1) the Neer test – full flexion of the shoulder with scapula stabilized and applied overpressure produces pain; (2) the Hawkins-Kennedy test – with shoulder and elbow flexed to 90°, internal rotation of the shoulder is performed with overpressure producing pain; (3) the painful arc test – active abduction of shoulder noting pain from 60° to 120°; (4) the external rotation resistance test (ERRT) – with shoulder completely abducted and elbow flexed to 90°, medial pressure is applied to forearm producing resisted shoulder external rotation with weakness if positive; and (5) the empty can test – with shoulder at 90° of flexion in the scapular plane with elbow straight and thumb pointing at the floor, downward pressure applied to wrist producing weakness if positive. The Neer test, painful arc test, and ERRT were useful individually in ruling out SAIS. Performing 5 tests of shoulder function with <3 being positive was also useful in ruling out SAIS. To rule in SAIS, the painful arc, ERRT, and empty can tests were useful.

**Reviewer's Comments:** This study helps inform the utility of physical diagnosis skills in diagnosing shoulder pain and SAIS in particular. Results are limited by the combination pathology found at arthroscopy, which colors the specificity of these diagnostic maneuvers for SAIS. (Reviewer-Peggy Schlesinger, MD).

© 2010, Oakstone Medical Publishing

Keywords: Shoulder Pain, Subacromial Impingement
Atherosclerosis may be accelerated by development of pro-inflammatory HDL in patients with antiphospholipid antibody syndrome.

**Background:** In normal subjects, HDL is known to be protective in the development of atherosclerosis. However, HDL in the setting of low-grade systemic inflammation may lose its protective properties and become more pro-inflammatory, thus promoting atherosclerosis. Since atherosclerotic disease is a complication of chronic systemic inflammatory diseases such as rheumatoid arthritis, could HDL be atherogenic in these diseases?

**Objective:** To present new information on vasculopathy in antiphospholipid antibody syndrome (aPL) patients that might change our understanding of the relationship of HDL to atherosclerotic disease. **Discussion:** aPL patients have antibodies to anticardiolipin and antiphospholipids, and they have an increased tendency to form clots, both venous and arterial. These patients also have accelerated atherosclerosis, similar to that seen in chronic systemic low-grade inflammatory diseases. What might be the mechanism of this accelerated vascular disease in these patients? Paraoxonase is an antioxidant enzyme related to HDL that has an important role in defense against lipid peroxidation. Prior research has shown that levels of paraoxonase are inversely related to anticardiolipin antibody levels in aPL patients. aPL patients are also known to make antibodies targeted at HDL.

**Participants:** 77 aPL+ women seen at a lupus outpatient clinic between June 2006 and April 2009 were investigated in this study and were compared to 77 matched controls, mainly friends and clinic employees.

**Methods:** Cases and controls were matched for age, sex, and cardiovascular risk factors. aPL+ patients had significant titers of IgG and IgM anticardiolipin antibodies, with lupus anticoagulant activity demonstrated on at least 2 occasions 12 weeks apart. Lupus patients and patients with other vasculopathy were excluded.

**Results:** Of 77 aPL+ patients, 38 had had a thrombotic event, 23 had >3 miscarriages and/or fetal death in the past, and 16 had only aPL without clinical correlates. Serum levels of paraoxonase, aPL antibody levels, and HDL were determined, and carotid intima media thickness (CIMT), flow-mediated dilatation, and pulse wave velocity were measured to evaluate structural and functional arterial abnormalities in all patients. Significant differences were seen with aPL women compared to controls in these areas: paraoxonase levels were higher in controls ($P < 0.005$), lipoprotein levels were higher in controls ($P < 0.046$), flow-mediated dilatation was higher in controls ($P < 0.001$), and CIMT was lower in controls ($P < 0.001$). The level of HDL was not different in the 2 groups; however, HDL in aPL patients has a "pro-atherogenic phenotype" that is ineffective at inhibiting inflammation and does not function as an antioxidant, whereas the control HDL retained its anti-inflammatory and antioxidant properties.

**Reviewer's Comments:** aPL patients have an aberrant atherogenic HDL and decreased paraoxonase activity with measurable structural vascular changes compared to controls. These intriguing findings could instruct future efforts to understand and abrogate atherosclerosis in other chronic systemic inflammatory diseases. (Reviewer-Peggy Schlesinger, MD).

© 2010, Oakstone Medical Publishing

Keywords: Antiphospholipid Antibody Atherosclerosis, Paraoxonase

Print Tag: Refer to original journal article
In this preliminary study, fish-derived omega-3 fatty acids may improve outcomes of patients with cardiovascular disease by slowing the aging of cells.

**Background:** Omega-3 fatty acids from fish sources have been shown to improve morbidity and mortality in patients with cardiovascular disease. The mechanism of this benefit is not known. Telomeres form a protective cap on the ends of chromosomes, and telomere shortening is being used as a marker for biological age. Short telomeres have been linked to poor cardiovascular outcomes.

**Objective:** To determine if omega-3 fatty acid levels can predict telomere shortening over time in a population of patients with cardiovascular disease.

**Design:** Prospective cohort study.

**Participants/Methods:** Subjects were part of the Heart and Soul Study, which is a study evaluating psychosocial factors in patients with known, stable coronary artery disease (CAD). In addition to baseline examinations and questionnaires, venous blood samples were drawn on entry into the trial and at 5 years. Samples were analyzed for many things including omega-3 fatty acids DHA (docosahexaenoic) and EPA (eicosapentaenoic) levels and leukocyte telomere length. Omega-3 fatty acid levels were divided into quartiles.

**Results:** 608 participants were included in the analysis. Most were men with an average age of 66 years. Baseline omega-3 fatty acid levels did not predict baseline telomere length. In multivariate analysis, there was a linear relationship between baseline omega-3 fatty acid levels and telomere shortening. There was significantly more telomere shortening over 5 years in the lowest quartile of baseline fatty acid levels compared to the highest quartile.

**Conclusions:** Telomere shortening has been shown independently to predict outcomes in patients with cardiovascular disease. This study found slower telomere shortening in CAD patients with the highest baseline marine omega-3 fatty acid levels. Omega-3 fatty acids may work by slowing cellular aging.

**Reviewer's Comments:** To this point, we have not understood how fish and fish oil provide benefit in patients with heart disease. This preliminary study suggests that one of the mechanisms may be by slowing the aging of cells. Whether this is unique to patients with CAD will require further investigation. (Reviewer-Deborah L. Greenberg, MD).

© 2010, Oakstone Medical Publishing

Keywords: Omega-3 Fatty Acids, Benefits, Telomeric Aging, Coronary Heart Disease

Print Tag: Refer to original journal article
The Revised Cardiac Risk Index -- Still Getting the Job Done

Systematic Review: Prediction of Perioperative Cardiac Complications and Mortality by the Revised Cardiac Risk Index.
Ford MK, Beattie WS, Wijeysundera DN:
Ann Intern Med 2010; 152 (January 5): 26-35

The Revised Cardiac Risk Index performs moderately well in discriminating between patients at low and high risk for cardiac events after noncardiac surgery.

**Background:** The Revised Cardiac Risk Index (RCRI) is a widely used tool for estimation of cardiac risk perioperatively for noncardiac surgery.

**Objective:** To evaluate the ability of the RCRI to discriminate between patients who are at low and high risk for cardiac complications when undergoing noncardiac surgery

**Design:** Systematic review using MEDLINE, EMBASE, and ISI Web of Science (1966 to 2008).

**Methods:** 2 reviewers independently reviewed all cohort studies that reported RCRI score and reported major cardiac complications including myocardial infarction, cardiac arrest, and cardiac death, as well as all-cause death.

**Results:** 24 cohort studies (representing 792,740 patients) were identified; 18 of these reported cardiac complications. Of these, only 6 were prospective and had a clear method for outcome surveillance, as well as blinded outcome adjudication (and 1 of these 6 studies was the original study from which the RCRI was derived). The RCRI discriminated moderately well between patients at low versus high risk for cardiac complications (area under the curve [AUC], 0.75; sensitivity, 0.65; specificity, 0.76; positive likelihood ratio [LR], 2.78; and negative LR, 0.45). The RCRI performed less well on the subset of patients who underwent vascular noncardiac surgery (AUC, 0.64; sensitivity, 0.70; and specificity, 0.55).

**Conclusions:** The RCRI continues to be a reasonable tool for predicting of perioperative cardiac risk, although it is less accurate among patients undergoing vascular surgery.

**Reviewer's Comments:** We frequently use prediction tools such as the RCRI to help guide our patients in medical decision making. This study puts the RCRI to the test by looking back in the perioperative literature to see how accurately it determines which patients are at risk for cardiac complications. For me, it is reassuring to see that the RCRI actually does a reasonably good job, and it gives me more confidence in sharing these numbers with my patients. Still, we are in need of more research and publications in perioperative medicine aimed at creating more sophisticated measurements of perioperative risk. Until then, the RCRI is a reasonable tool to support education and decision making in daily practice. (Reviewer-Molly Blackley Jackson, MD).

© 2010, Oakstone Medical Publishing

Keywords: Revised Cardiac Risk Index, Perioperative Complications, Mortality

Print Tag: Refer to original journal article
An Aspirin a Day Isn’t Always the Answer

Aspirin for Primary Prevention of Cardiovascular Events in People With Diabetes: Meta-Analysis of Randomised Controlled Trials.

De Berardis G, Sacco M, et al:

BMJ 2009; 339 (November 6): b4531

Do not start aspirin therapy for primary prevention of cardiovascular events in patients with diabetes empirically, rather calculate each patient's cardiac risk to better weigh benefits and harms.

Background: Until December 2009, the American Diabetes Association has recommended aspirin for primary prevention of cardiovascular disease for all patients aged >30 years with diabetes. The efficacy of aspirin for primary prevention of cardiovascular disease has been shown in higher-risk populations, but in a recent meta-analysis, the subgroup of patients with diabetes showed no cardiovascular protection.

Objective: To evaluate the efficacy of aspirin for primary prevention of cardiovascular disease in patients with diabetes.

Design: Meta-analysis of randomized placebo-controlled trials.

Participants: Diabetic patients with no known cardiovascular disease (1 study with 10% of patients with known cardiovascular disease).

Methods: Studies included in the meta-analysis were open, blinded, randomized controlled trials of patients with diabetes with mixed cardiovascular risks using aspirin compared to placebo or no therapy. Outcomes of interest were all-cause mortality, death from cardiovascular etiologies, nonfatal myocardial infarction (MI), and nonfatal stroke.

Results: 6 trials, representing 10,117 people, were included. The dose of aspirin ranged from 100 mg every other day to 650 mg/day, and duration of therapy ranged from 3.6 to 10.0 years. Aspirin use did not show a significant decrease in major cardiovascular events (relative risk [RR], 0.9; 95% CI, 0.81 to 1.00; \( P =0.06 \)), MI (RR, 0.86; 95% CI, 0.61 to 1.21), stroke (RR, 0.83; 95% CI, 0.6 to 1.14), death from cardiovascular causes (RR, 0.94; 95% CI, 0.72 to 1.23), or all-cause mortality (RR, 0.93; 95% CI, 0.82 to 1.05). There was significant heterogeneity in the nonfatal MI results. Aspirin significantly reduced the risk of nonfatal MI in men (RR, 0.57; 95% CI, 0.34 to 0.94) but not in women (RR, 1.08; 95% CI, 0.71 to 1.65). There was no statistically significant evidence of increased bleeding, gastrointestinal bleeding, or gastrointestinal symptoms with use of aspirin compared to placebo.

Conclusions: Aspirin showed no benefit over placebo for primary prevention of cardiovascular disease in patients with diabetes without known cardiovascular disease.

Reviewer's Comments: The authors speculated that the nearly significant reduction in major cardiovascular events suggested that aspirin either had a low efficacy and/or that the studies were underpowered to detect this smaller benefit. They postulated that there are likely unique mechanisms for vascular events in patients with diabetes. From a practical perspective, each provider must calculate risks and benefits for each patient, understanding that, at best, if aspirin garners a 10% relative risk reduction in cardiovascular events, the number needed to treat is 1000 per year to prevent 1 to 2 cardiovascular events, which is equal to the number needed to harm of 1000 for major bleeding events reported in other studies. I plan to be more thoughtful in my initiation of aspirin in this population and to use tools like the Framingham cardiac risk calculator to select patients with a >20% 10-year risk of cardiac events. I would weigh against the increased risk of bleeds in people aged >70 years. (Reviewer-Genevieve L. Pagalilauan, MD).

© 2010, Oakstone Medical Publishing

Keywords: Diabetes, Cardiovascular Events, Aspirin, Primary Prevention

Print Tag: Refer to original journal article
The Prevalence of Clinically Relevant Incidental Findings on Chest Computed Tomographic Angiograms Ordered to Diagnose Pulmonary Embolism.

Hall WB, Truitt SG, et al:


Chest CTA Is Valuable Test, but Use Judiciously for PE

Background: Patients presenting with suspected pulmonary embolism (PE) often undergo chest CT angiography (CTA). While chest CTAs can reveal PEs as well as alternative findings that may account for a patient’s symptoms, they also uncover incidental findings that can cause significant anxiety and lead to additional radiologic studies and diagnostic interventions.

Objective: To determine the prevalence of PE and of alternative diagnoses for patients undergoing pulmonary CTA who present to the emergency department (ED) with clinical scenarios concerning for PE, and to determine the prevalence and management implications of incidental findings.

Design: Cross-sectional study.

Methods: 589 chest CTAs ordered from the ED of a single tertiary care hospital were reviewed to determine the prevalence of PE, alternative findings to explain acute symptoms, incidental findings that required further diagnostic imaging (masses/nodules, significant adenopathy), or clinical follow-up and incidental findings that required less urgent or no follow-up (atelectasis, emphysema, cardiomegaly, bone findings, atherosclerotic changes).

Results: Mean age of patients was 53 years (range, 34 to 72 years); 63% were women. Of 589 patients who underwent CTA, 55 (9%) had a PE; 487 (81%) had findings other than PE. There were 195 patients (33%) who had diagnoses other than PE that could explain their presenting symptoms including pulmonary infiltrates (n=66) and pleural effusions (n=113). Thirty-five percent of infiltrates and 67% of pleural effusions were large enough to be seen on chest x-ray. There were 615 incidental CTA findings including pulmonary nodules (122), pulmonary masses (24), mediastinal masses (21), and adenopathy (220). Of patients, 141 (24%) had incidental findings requiring further follow-up. Seventy-three chest CTAs revealed new pulmonary nodules, of which 78% led to recommendations for follow-up with CT, 2% with PET scan, 2% with bronchoscopy, 2% with mediastinoscopy, and 8% with other procedures. A total of 122 patients (20%) had a D-dimer assay and, of these, 24 (20%) were negative. None of the patients with negative D-dimer assays had CTA findings of PE.

Reviewer’s Comments: Chest CTAs to evaluate patients for acute PE in the emergency department are more than twice as likely to find an incidental pulmonary nodule or adenopathy than they are to find a pulmonary embolism. Incidental findings lead to both anxiety and further diagnostic testing and radiation exposure. In addition, they often require close follow-up by the primary care provider or a pulmonologist. While chest CTA is a valuable test, the results of this study should cause us to order this test judiciously in carefully selected patients and in accordance with evidence-based guidelines for diagnosing suspected PE. The ease of obtaining a CTA should not be the driving factor. When a chest CTA is indicated, patients should be informed about the implication of potential incidental findings. (Reviewer-Ellaine F. Sachter, MD).

© 2010, Oakstone Medical Publishing

Keywords: Pulmonary Embolism, Chest CT Angiograms, Incidental Findings

Print Tag: Refer to original journal article
Almost 10% of patients with hemoptysis and a normal chest x-ray have a respiratory tract malignancy.

**Background:** Hemoptysis is a common and disturbing symptom. It can be a symptom of a life-threatening disease such as lung cancer, or it can be associated with something as benign as bronchitis. Early diagnosis of lung cancer is crucial if there is any hope of surgical cure. The optimal workup of patients with hemoptysis and normal chest radiographs is unclear.

**Objective:** To determine whether further workup of patients with hemoptysis and a normal chest x-ray is warranted.

**Design/Methods:** Retrospective study of 275 episodes of hemoptysis in patients with a normal chest x-ray that occurred over a 56-month period. All of these patients received a chest CT scan and fiberoptic bronchoscopy.

**Results:** A total of 275 episodes of hemoptysis in patients with normal chest x-rays occurred in 270 patients. Mean age of patients was 60 years. Of 270 patients, 246 were either active smokers (156) or ex-smokers (90). Twenty-six patients (9.6%) were diagnosed with respiratory tract malignancies (22 of these were lung cancers). Of patients with cancer, 85% were smokers. The most common cause of hemoptysis in this study was acute bronchitis (63%). Chest CT was suggestive of cancer in 96% of patients with malignancy.

**Conclusions:** Almost 10% of patients with hemoptysis with a normal chest x-ray have cancer. Almost all of these are suggested on chest CT scan.

**Reviewer's Comments:** This study addresses a common problem in primary care. How extensive a workup should be done for hemoptysis? It is a common problem. In this study, the majority of patients had bronchitis (a very common problem) as the cause for their hemoptysis. The finding that almost 10% of those with a normal x-ray had cancer is concerning. In this study, only 8 of 26 patients had cancer that was resectable. Because chest CT scans suggested cancer in almost all patients who had cancer, I think I will obtain a chest CT scan on any patient with a recent smoking history and hemoptysis with a normal chest x-ray. If the CT is normal, I do not think I would refer the patient for bronchoscopy immediately. (Reviewer-Douglas S. Paauw, MD).

© 2010, Oakstone Medical Publishing

Keywords: Hemoptysis, Chest CT Scan

Print Tag: Refer to original journal article
Amiriptyline and pregabalin both work equally well for diabetic neuropathy, but pregabalin has fewer side effects and is dramatically more expensive.

**Background:** Diabetic neuropathy is a common and difficult problem in patients with longstanding diabetes. Treatment of diabetic neuropathy is targeted at providing pain relief. For many years, tricyclic antidepressants were the mainstay of treatment of diabetic peripheral neuropathy. In recent years, gabapentin and more recently pregabalin have been widely used to treat diabetic peripheral neuropathy.

**Objective:** To compare the safety and efficacy of amitriptyline and pregabalin in the treatment of diabetic neuropathy.

**Design:** Randomized, double-blind crossover trial.

**Methods:** Patients titrated the dose of the drug as needed, with the following doses used: amitriptyline 10, 25, and 50 mg once daily or pregabalin 75, 150, and 300 mg twice daily. A placebo washout period of 3 weeks was used between drugs. In total, 44 patients completed the study. Assessment by questionnaire on pain relief, overall improvement, and adverse events was recorded.

**Results:** There was no statistically significant difference in pain relief between amitriptyline and pregabalin. While on amitriptyline, 34% reported good pain relief compared to 48% when on pregabalin. Patients’ global impression of change was 73% improved with amitriptyline and 77% with pregabalin. Side effects were more common with amitriptyline, with tiredness being the most common symptom, in 11% of patients on amitriptyline compared to none while on pregabalin. Increase in sleep duration was more common in patients on amitriptyline (41%) compared to 14% on pregabalin. Amitriptyline was discontinued by 39% of patients and pregabalin by 14%. Pregabalin was preferred by 43% of patients and amitriptyline by 34%.

**Conclusions:** Amitriptyline and pregabalin have similar efficacy, with amitriptyline having more side effects.

**Reviewer’s Comments:** This study is a well-done head-to-head comparison of 2 effective treatments for diabetic neuropathy. It is rare to find head-to-head studies of effective treatments. The randomized crossover design is also attractive. What did we learn? Pregabalin is slightly preferred and has fewer side effects and equal efficacy to amitriptyline. There was a much higher rate of stopping the medication in the amitriptyline arm. I was surprised how few classic anticholinergic side effects were reported (<10% of those receiving amitriptyline had dry mouth, orthostatic hypotension, dizziness, or urinary retention). This study carefully excluded patients who are at higher risk for complications of tricyclics (those with complicated medical illness). The optimal dose for pregabalin was 150 mg twice daily. The monthly cost of 150 mg twice daily of pregabalin is $168 compared to $4 per month for amitriptyline. (Reviewer-Douglas S. Paauw, MD).

© 2010, Oakstone Medical Publishing

Keywords: Diabetic Neuropathy, Amitriptyline, Pregabalin

Print Tag: Refer to original journal article
High-Flow O₂ Effective for Cluster Headache


Cohen AS, Burns B, Goadsby PJ:

JAMA 2009; 302 (December 9): 2451-2457

In patients with cluster headache, high-flow oxygen effectively reduces pain and associated symptoms and decreases need for rescue medicine.

Background: Cluster headaches are attacks of extreme unilateral pain in the periorbital region or temple, often with cranial autonomic symptoms. Prevalence in the general population is 0.3%, with a male:female ratio of 2.5:1. Treatment of acute attacks is typically with subcutaneous sumatriptan. A handful of small studies have shown benefit of oxygen in this setting, but its efficacy has not been well established.

Objective: To evaluate high-flow oxygen versus placebo in the treatment of cluster headache.

Design: Double-blind, randomized, placebo-controlled crossover trial.

Participants/Methods: Patients were adults with a prior diagnosis of episodic or chronic cluster headache; exclusion criteria included chronic migraine, pregnancy, chronic obstructive pulmonary disease, and prior use of oxygen therapy. Follow-up was for 4 cluster headache attacks. Each subject was sent home with 2 blinded cylinders, labeled treatment 1 and treatment 2 (oxygen for 100% high-flow and room air to be delivered at 15 L/minute). Subjects were instructed to administer gas from 1 canister for the first attack, switch to the other tank for the second, then crossing back to the first tank for 2 more attacks. Randomization of cylinders determined the order in which the cylinders should be used. Patients gave self-reports of pain and severity at 15, 20, 30, and 60 minutes; overall response; overall functional disability; effect on associated symptoms; and need for other rescue medicine.

Results: 334 patients were assessed for eligibility, 109 were randomized, and 76 received treatment. In total, 78% of cluster headache attacks treated with high-flow O₂ resulted in the subject being pain free at 15 minutes as compared with 20% of those treated with air. Markedly fewer episodes treated with high-flow oxygen had to be treated with rescue medications (28% vs 53%). Flares treated with oxygen resulted in 60% improvement in overall functional disability versus 15% after air treatments. No adverse events were reported with either treatment.

Conclusions: High-flow oxygen is an effective and safe treatment for cluster headache, and should be standard of care.

Reviewer’s Comments: Though standard guidelines in the neurology literature already recommend oxygen for treatment of cluster headaches, there was previously a dearth of large randomized trials to help confirm the efficacy of this treatment. This fairly large, well-designed trial clearly supports the use of high-flow oxygen as first-line therapy. Further, it suggests that a large proportion of patients with cluster headaches may avoid rescue medications by starting early treatment with oxygen. These data are especially helpful for patients in whom triptans are contraindicated, as they provide solid evidence for this triptan alternative. (Reviewer-Molly Blackley Jackson, MD).

© 2010, Oakstone Medical Publishing

Keywords: Cluster Headache, Oxygen

Print Tag: Refer to original journal article
Reduced Salt Intake Decreases Stroke, Cardiovascular Risks

Salt Intake, Stroke, and Cardiovascular Disease: Meta-Analysis of Prospective Studies.

Strazzullo P, D’Elia L, et al:

BMJ 2009; 339 (November 24): b4567

In patients with a high-salt diet, reducing sodium intake by 5 g/day (1 teaspoon) can reduce the risk for stroke and cardiovascular events.

**Background:** Salt has long been recognized as a contributor to elevated blood pressure and hypertension. Most providers advise patients to follow an AHA or DASH diet if they have hypertension or coronary artery disease. However, is there sufficient evidence for cardiovascular benefit to recommend a lower-salt diet in the general population?

**Objective:** To determine the association between "habitual salt intake" and stroke and cardiovascular disease.

**Design:** Meta-analysis of prospective studies.

**Methods:** A systematic review identified 13 studies representing >177,000 adults who met inclusion criteria of being a prospective population study, which assessed intake of salt as a baseline exposure, followed participants >3 years, and reported stroke and/or cardiovascular outcomes stratified by salt intake. Average study quality score was 15.5 on a scale of 19.0 (range, 12.0 to 18.0), suggesting higher-quality studies were included. Salt intake was categorized as "low salt" and "high salt" with a difference of 5 g/day of sodium between groups. Pooled relative risks (RRs) were calculated for each outcome and were stratified by salt intake.

**Results:** The higher-salt intake group had an increased RR of stroke (1.23; 95% CI, 1.06 to 1.43) and a strong trend toward higher cardiovascular outcomes (RR, 1.14; 95% CI, 0.99 to 1.32; P = 0.07). When 1 outlier study was excluded in the cardiovascular analysis, results became significant (RR, 1.17; 95% CI, 1.02 to 1.34). There was marked heterogeneity among studies, but funnel plot analysis showed no publication bias. In 3 studies that reported out men and women separately, women showed a stronger association with higher salt intake for both stroke and cardiovascular outcomes than did men. For men and women, stroke outcomes had an RR of 1.30 (95% CI, 0.64 to 2.65) and 1.56 (95% CI, 1.14 to 2.13), respectively, and cardiovascular outcomes had an RR of 1.31 (95% CI, 0.97 to 1.77) and 1.27 (95% CI, 1.05 to 1.55), respectively. Interestingly, adjustment for baseline blood pressure and hypertension status yielded similar results to the total meta-analysis.

**Conclusions:** A reduction in salt intake of approximately 5 g/day (1 teaspoon) is associated with a 23% reduction in stroke and 17% reduction in cardiovascular outcomes.

**Reviewer’s Comments:** This study increases our confidence that sodium intake can affect hard outcomes like stroke and heart attack, and not just blood pressure. Moreover, the data suggest an independent effect of a lower-salt diet that stands apart from baseline blood pressure and weight. Despite arguments that we could tailor our recommendations more elegantly to patients by considering individual salt sensitivity differences, baseline risk factors, and perhaps gender and ethnic background, it makes good sense for population-based medicine to recommend that all adult patients with high-salt diets reduce their sodium intake by 1 teaspoon each day (5 g/day). (Reviewer-Genevieve L. Pagalilaauan, MD).

© 2010, Oakstone Medical Publishing

Keywords: Salt Intake, Stroke, Cardiovascular Disease Risk

Print Tag: Refer to original journal article
G127V confers resistance to kuru infection and is not seen in patients with kuru or in other populations outside the area of Papua New Guinea.

**Discussion:** The first reports of kuru from New Guinea appeared in the early 20th century. Kuru is caused by a prion protein that is transmitted via ritual cannibalism of deceased relatives practiced by women and young children in the Fore linguistic groups in the Eastern Highlands Province of Papua New Guinea. Ritual cannibalism ceased in the late 1950s, and the disease has disappeared from the youngest Fore villagers. Researchers were able to do genetic profiling of >3000 persons from the area, including 709 who participated in "mortuary feasts" and 152 who died of kuru. Through this mechanism, they were able to show the appearance of a novel prion gene variant -- G127V -- that occurred in half the women in the endemic area with genetic susceptibility to infection. This new variant confers resistance to kuru infection, and is not seen in patients with kuru or in other populations outside this endemic area.

**Reviewer's Comments:** Kuru is a lethal prion disease transmitted by cannibalism occurring in a specific isolated geographic area of Papua New Guinea. The geographical restriction of the kuru epidemic and the limited population in the area with very little migration or racial intermixing has allowed these researchers to document genetic drift and the appearance of prion resistance factors -- heterozygosity (GV) at codon 127 and (MV) at codon 129 of the prion protein gene -- that are protective against the epidemic of lethal infection with the prion-causing kuru. This genetic polymorphism is an example of the appearance of a genetic disease-resistance factor in this population occurring in response to natural selection pressures in a kuru endemic area. This is a truly remarkable landmark article that describes in detail the natural selection process occurring in the human genome in response to environmental pressure. This area of Papua New Guinea is our human Galapagos and these authors are our medical Darwins. (Reviewer-Peggy Schlesinger, MD).

© 2010, Oakstone Medical Publishing

Keywords: Genetics, Evolution, Neurodegenerative Disorders, Kuru Exposure

Print Tag: Refer to original journal article
Higher levels of physical activity are associated with a lower risk for rapid decline in kidney function among older adults.

**Background:** Physical activity is associated with metabolic benefits that decrease the risk of cardiovascular disease and stroke and may likewise have protective effects on the kidneys.

**Objective:** To determine if greater levels of physical activity are associated with a decreased incidence of declining kidney function in older adults.

**Design:** Longitudinal cohort study.

**Participants/Methods:** Study participants were 4011 individuals aged ≥65 years who were enrolled in the Cardiovascular Health Study (CHS) and who had completed at least 2 measurements of kidney function over 7 years. Physical activity (PA) scores (ranging from 2 to 8) were calculated by adding kilocalories (kcal) expended per week (ordinal score of 1 to 5 from quintiles of kcal per week) and walking pace (ordinal score for categories of <2, 2 to 3, and >3 mph). Estimated glomerular filtration rate (eGFR) was calculated using longitudinal measurements of cystatin C levels. Rapid decline in kidney function (RDKF) was defined as a decrease in eGFR of >3.0 mL/minute/1.73 m² per year. Covariates including age, sex, race, cardiovascular disease, diabetes, medications, smoking, alcohol use, body mass index, and blood pressure were determined through interviews, physical and laboratory examinations, and medical record review.

**Results:** RDKF occurred in 958 participants (23.9% or 4.1 events per 100 person-years). The highest PA group (score of 8) had an estimated risk for RDKF of 16% compared to 30% in the lowest PA group (score of 2). After multivariate adjustment, the 2 highest PA groups (scores of 7 to 8) had a 28% lower risk for RDKF (95% confidence interval, 21% to 41% lower risk) compared with the 2 lowest PA groups (score of 2 to 3). Further adjustment for measures of subclinical disease including carotid intimal thickness, impaired fasting glucose levels, and ankle arm index did not alter the results. Both exercise intensity (walking pace) and energy expenditure (kcal expended per week) were associated with lower incidence of RDKF. The association between PA level and RDKF was similar in subgroups of participants with baseline eGFRs of <60, 60 to 90, and 90 to 119 mL/minute/1.73 m².

**Conclusions:** Higher levels of PA are associated with a lower risk of RDKF among older adults.

**Reviewer's Comments:** Greater levels of physical activity among older adults were associated with a lower risk of RDKF after adjusting for clinical and subclinical covariates and regardless of baseline GFR. A strength of the study was the use of cystatin C levels to estimate changes in eGFR rather than serum creatinine, which depends on muscle mass which declines with age and may be affected by exercise. The study population was older and therefore the results cannot be generalized to younger populations. With the increasing burden of chronic kidney disease, the potential for exercise to slow or prevent its development has far-reaching public health benefits. The findings from this study add to the growing list of the health benefits of exercise. (Reviewer-Elaine F. Sachter, MD).

© 2010, Oakstone Medical Publishing

Keywords: Physical Activity, Renal Function

Print Tag: Refer to original journal article
This study found that, in adolescents and young adults without chronic kidney disease, detrimental effects of blood lead levels on estimated glomerular filtration rate occurred at levels <10 µg/dL, which is the current level of concern designated by the CDC.

**Background:** High levels of lead exposure are known to result in chronic kidney disease (CKD). The effect of low-level environmental lead exposure on kidney function in people without CKD, particularly in children, is unknown. The Centers for Disease Control and Prevention lowered its level of concern for lead levels in children from 30 µg/dL to 10 µg/dL in 1991 when studies raised concerns for adverse neurodevelopmental effects at levels as low as 10 µg/dL. Levels <10 µg/dL have been associated with adverse cardiovascular and cognitive effects, but the influence on kidney function has been difficult to ascertain due to limitations in detecting early declines in the glomerular filtration rate (GFR) due to the high variability of serum creatinine levels.

**Objective:** To examine the association between lead exposure and kidney function in a sample of U.S. adolescents.

**Design:** Retrospective cohort study.

**Methods:** 769 adolescents who participated in the Third National Health and Nutrition Examination Survey had their whole blood lead levels measured and renal function assessed using both the cystatin C-based and creatinine-based estimations of GFR (eGFR). Cystatin C levels, newer and more sensitive markers of kidney function, were measured in stored serum samples.

**Results:** 99% of participants had lead levels <10 µg/dL. The mean lead level was 1.5 µg/dL. The mean cystatin C-eGFR was 112.9 mL/minute/1.73 m2. After controlling for factors that can affect GFR and/or lead levels, higher lead levels were associated with reductions in cystatin C eGFR. Participants in the highest quartile for blood lead levels (>3.0 µg/dL) had a 6.6 mL/minute/1.73 m2 lower eGFR than participants who were in the lowest quartile for lead levels (<1 µg/dL). Lead levels were also associated with reductions in creatinine-based eGFR, but the association was weaker and was not statistically significant.

**Reviewer’s Comments:** Given the tremendous burden of CKD worldwide, it is critical to identify modifiable risk factors. The results of this study indicate that, in children and adolescents, small relative increases in blood lead levels may be associated with declining kidney function. Detrimental effects of blood lead levels on eGFR occurred at levels well beneath 10 µg/dL. Previous studies using creatinine-based eGFR may have underestimated the adverse effects of lead exposure on kidney function. Earlier studies have focused on high-risk populations or people with preexisting CKD, and in both cases, low level lead exposure was associated with reduced kidney function. This study indicates that low levels of lead exposure are also detrimental to renal function in a healthy population without CKD or risk factors for CKD. While the industrial use of lead had been largely eliminated, most of the U.S. population still has detectable blood levels. Inner city children and adults living in lower socioeconomic areas have higher lead levels. CKD disproportionately affects certain racial/ethnic groups and lower socioeconomic groups. Further studies are needed to understand if the increased risk is related in part to environmental lead exposure. (Reviewer-Elaine F. Sachter, MD).

© 2010, Oakstone Medical Publishing

Keywords: Lead Exposure, Kidney Function

Print Tag: Refer to original journal article
Increased Risk for VTE Lasts for Months Postoperatively

Background: Venous thromboembolic (VTE) disease in postsurgical patients is common and can be deadly. Duration and magnitude of risk for VTE postoperatively is not clear.

Objective: To better understand the risks of VTE after surgery.

Design: Prospective cohort study (Million Women Study).

Participants/Methods: 947,454 women in the National Health Service (NHS) England and Scotland database were recruited between 1996 and 2001. Exclusion criteria included known cancer at the time of enrollment, prior VTE or clotting disorder, or multiple surgeries during follow-up. Follow-up was approximately 6 years on average; investigators linked NHS data on hospital admissions and deaths to questionnaires submitted from patients.

Results: 239,614 women had surgery during follow-up; 5419 women were admitted to the hospital for VTE, and 270 deaths were attributed to VTE. Women who underwent surgery during follow-up were 70 times more likely than women who had not undergone surgery to be admitted for VTE within the first 6 weeks after an inpatient operation (relative risk [RR], 69.1; 95% CI, 63.1 to 75.6) and 10 times more likely after outpatient (day case) surgery (RR, 9.6; 95% CI, 8.0 to 11.5). In the 7 to 12 weeks after surgery, risks were still increased (RR, 19.6; 95% CI, 16.6 to 23.1 for inpatient cases and RR, 5.5; 95% CI, 4.3 to 7.0 for outpatient cases). Among all VTE cases, slightly more cases of pulmonary embolism were identified (2487) than deep venous thrombosis (3529). The highest risk for postoperative VTE was after hip or knee replacement (RR, 220.6), cancer (RR, 91.6), fracture (RR, 89.0), and vascular surgery (RR, 87.0).

Conclusions: Risk for VTE is markedly increased in the first 12 weeks after surgery; the degree of increased risk varies widely by type of surgery and diagnosis. This increase in risk is seen in both inpatient and outpatient surgery cases.

Reviewer’s Comments: This study demonstrates an increase in risk for postoperative VTE for much longer than originally suspected for all types of surgeries (not just total hips and knees). I was most surprised to learn that outpatient day surgery carries a significantly increased risk of VTE. It would have been very helpful to know which patients received perioperative DVT prophylaxis and to what degree that decreased their risk, but unfortunately, that information was not available to these researchers in the study data. A randomized trial to more clearly elucidate optimal duration of prophylaxis in high-risk postsurgical patients would be a helpful follow-up to this study. (Reviewer-Molly Blackley Jackson, MD).

© 2010, Oakstone Medical Publishing

Keywords: Venous Thromboembolism, Postoperative Risk

Print Tag: Refer to original journal article
Statins May Decrease Risk of VTE in Cancer Patients

Statins Decrease the Occurrence of Venous Thromboembolism in Patients With Cancer.
Khmasuwan D, Divietro ML, et al:
Am J Med 2010; 123 (January): 60-65

Statin use is associated with a reduced risk of venous thromboembolism in cancer patients.

**Background:** The risk for venous thromboembolism (VTE) is increased in patients with malignancy. Recent studies suggest a link between dyslipidemia and VTE. Other studies have suggested that statins may reduce the risk of VTE through their effect on lipids and the vascular endothelium.

**Objective:** To determine if there is an association between use of statins and the incidence of VTE in a high-risk patient population with solid organ malignancy.

**Design:** Retrospective case-controlled study.

**Participants/Methods:** All patients with a history of solid organ tumor and at least 2 admissions to an academic medical center over a 3-year period were eligible for the study. Risk factors for VTE and medical comorbidities were determined. Patients were stratified into 2 groups: those on a statin medication for at least 2 months prior to admission and those who had never used statins or had used them for <2 months (controls). A diagnosis of deep venous thrombosis (DVT) or pulmonary embolism (PE) during the 3-year period was the primary end point.

**Results:** 740 patients were included in the evaluation. Mean age was 65 years, and 52% were women; 26% of patients were taking statins. Eighteen percent of patients were diagnosed with VTE. In logistic regression models, use of statin medication was associated with a reduced risk of VTE (odds ratio, 0.33; 95% CI, 0.19 to 0.59; \( P < 0.001 \)). Among patients on statins, 8% developed VTE compared to 21% of controls.

**Conclusions:** This retrospective study suggests that statin use may reduce the risk for VTE in hospitalized patients with a history of solid organ malignancy.

**Reviewer's Comments:** This study was quite intriguing. We have long postulated other uses for statin medication beyond their cardiovascular primary and secondary protective benefits. A randomized controlled trial is needed to determine if this class of medication may be helpful in the primary prevention of VTE in cancer patients. (Reviewer-Deborah L. Greenberg, MD).

© 2010, Oakstone Medical Publishing

Keywords: Cancer, Venous Thromboembolism, Statins

Print Tag: Refer to original journal article
Primary-Care Physicians Can Reduce Binge Drinking

Efficacy of Physician-Delivered Brief Counseling Intervention for Binge Drinkers.


A brief, 2-visit intervention by a patient's physician can make a big impact on binge drinking behavior.

**Background:** Binge drinking is prevalent in the U.S. and a major cause of accidents and other adverse events. Binge drinking is defined as >5 drinks for men or 4 drinks for women over approximately a 2-hour time period. There have been inconsistent reports on the impact of brief interventions on binge drinking behavior.

**Objective:** To test the efficacy of brief, multi-contact, behavioral counseling in the primary care setting on binge drinking.

**Design:** Randomized controlled trial.

**Participants/Methods:** Patients aged 18 to 65 years were identified from 20 family physician-based, primary care centers in Madrid. Patients were screened using the Alcohol Use Disorders Identification Test (AUDIT), and binge drinkers were invited to take part in an interview. Those qualified for the study were randomized to a brief physician intervention or routine care. The intervention was composed of 2 sessions (10 to 15 minutes each) 4 weeks apart during which the physician reviewed a scripted workbook. Information included health effects of alcohol, review of at-risk behavior, options for cutting back, and cognitive behavioral exercises. Patients were contacted by a nurse at 2 and 8 weeks after the intervention to review the information. The primary outcome was the frequency of binge episodes in the prior 30 days and the number of binge drinkers at 12 months.

**Results:** From a population of 15,325 patients, 2433 were binge drinkers based on the AUDIT. A total of 752 patients met inclusion criteria and were randomized to either the intervention group (n=371) or control group (n=381). Participants had similar baseline characteristics. Most were aged 31 to 40 years, in a relationship, and employed. There was a significant reduction in the number of binge episodes in the 30 days following counseling in the intervention group compared to the control group. Significantly more patients in the intervention group had no binge episodes (48%) compared to the control group (33%) during the follow-up period. The reduction was greatest over time among women in the treatment group.

**Conclusions:** A brief, physician-delivered intervention can significantly reduce binge drinking behavior.

**Reviewer's Comments:** Binge drinking is a common behavior that is often not identified or addressed in primary care practice. This study suggests that physicians can make a reasonable impact with a relatively easy intervention. (Reviewer-Deborah L. Greenberg, MD).

© 2010, Oakstone Medical Publishing

Keywords: Binge Drinking, Brief Counseling, Primary Care

Print Tag: Refer to original journal article
Chronic Opiate Therapy Increases Overdose Risk

Opioid Prescriptions for Chronic Pain and Overdose: A Cohort Study.

Dunn KM, Saunders KW, et al:


Risks of long-term opioid therapy are higher in certain subsets of patients and as the dose increases.

**Background:** A growing number of adults are taking long-term opioid therapy for the treatment of noncancerous chronic pain. The risk for overdose in this patient population has not been studied.

**Objective:** To determine the risk of fatal and non-fatal overdose in patients receiving chronic opioid therapy for noncancerous chronic pain, and to determine if the risk is dose related.

**Design:** Observational cohort study.

**Methods:** This study is part of the Consortium to Study Opioid Risks and Trends study using the Group Health Cooperative database of 500,000 individuals in the state of Washington. Subjects were adult patients started on chronic opioid medications for chronic noncancerous pain between 1997 and 2005. The average daily morphine equivalent dose over a 90-day period was calculated for each patient. Other comorbidities were collected for each patient. Fatal and nonfatal overdoses were identified through chart review and standardized criteria. The primary outcomes were fatal and nonfatal overdose and the average daily dose of medications.

**Results:** 9940 patients were followed up for an average of 42 months. The most common diagnoses were back pain and extremity pain. The average age was 54 years, and 60% of subjects were women. The average daily morphine equivalent was 13.3 mg. Only 10% of subjects were primarily on long-acting opioids. Three fourths of patients were prescribed a sedative-hypnotic at some time during follow-up. There were 6 fatal overdoses and 74 nonfatal overdoses during the follow-up period. The annual rate of fatal overdose was 17 per 100,000 person-years, and the annual rate of serious overdose was 116 per 100,000 person-years. Rates were higher in patients aged >65 years and in those with depression and a history of substance abuse. The risk of overdose increased with dose. Patients receiving >100 mg/day had a 9-fold increased risk (1791 per 100,000 person-years) of any overdose compared to those on the lowest doses. Most patients were taking lower doses; therefore, most overdoses occurred in patients on low to moderate doses.

**Conclusions:** Patients being treated with long-term opioid therapy for noncancerous pain are at risk for fatal and nonfatal overdose, especially those taking high doses.

**Reviewer's Comments:** This study emphasizes the need to carefully screen patients before initiation of chronic opioid therapy, limit the dose of these medications, and carefully monitor these patients. (Reviewer-Deborah L. Greenberg, MD).

© 2010, Oakstone Medical Publishing

Keywords: Chronic Pain, Management, Opioids, Overdose

Print Tag: Refer to original journal article
Human monoclonal antibodies to *Clostridium difficile* toxins A/B result in lower rates of recurrence of *C difficile* infection.

**Background:** *Clostridium difficile* infection continues to increase in prevalence, with associated morbidity and mortality. The emergence of hyper-virulent and antibiotic-resistant strains is worrisome, and researchers continue to seek treatment options.

**Objective:** To test the efficacy of directed human monoclonal antibodies against *C difficile* toxins A and B, in addition to antibiotics, in patients with symptomatic *C difficile*.

**Design:** Randomized, double-blind, placebo-controlled trial.

**Methods:** Patients with symptomatic *C difficile* on antibiotic therapy with either metronidazole or vancomycin were randomized to treatment with a single infusion of 2 neutralizing human monoclonal antibodies against *C difficile* toxins A and B or to placebo (normal saline). The primary outcome was infection recurrence within 84 days of administration of placebo or monoclonal antibodies.

**Results:** 7396 patients were assessed for eligibility, 484 were screened, and 200 were enrolled from 30 participating facilities across the United States. Of these, 101 patients were randomized to receive antibody infusion, and 99 were randomized to placebo. Recurrence of *C difficile* was markedly lower among patients who received monoclonal antibodies (7% vs 25%; 95% CI, 7 to 29; *P* <0.001); the relative risk (RR) of recurrence was significantly lower in the antibody group (RR, 0.23; 95% CI, 0.08 to 0.54; *P* =0.01). Among patients with strain BI/NAP1/027, 8% of patients in the antibody groups had recurrence versus 32% in the placebo group (*P* =0.06). The intervention did not significantly affect the time to resolution, severity of diarrhea, or length of inpatient stay in the initial episode. Post hoc analysis revealed that fewer patients in the antibody arm were admitted to the hospital during follow-up (9% vs 20% in the placebo group; *P* =0.03). Serious adverse events were less frequent in the antibody group (18% vs 28%; *P* =0.09).

**Conclusions:** Monoclonal antibodies directed against *C difficile* toxins A and B appear effective and safe in reducing *C difficile* recurrence.

**Reviewer's Comments:** The results of this study are exciting and timely. Although further study is needed (this was a phase 2 trial), this research suggests we will soon have more tools for the secondary prevention of *C difficile*. Research is underway and is greatly needed in the area of primary prevention and in more effective treatment options to reduce the duration and severity of symptoms. (Reviewer-Molly Blackley Jackson, MD).
HbA₁c Correlates With Severity of OSA in Type 2 Diabetics

Impact of Untreated Obstructive Sleep Apnea on Glucose Control in Type 2 Diabetes.

Aronsohn RS, Whitmore H, et al:
Am J Respir Crit Care Med 2009; December 17 (): epub ahead of print

Type 2 diabetics with higher HbA₁c level and/or diabetic complications may be more likely to have undiagnosed or untreated sleep apnea.

**Background:** Obstructive sleep apnea (OSA) is known to impair glucose metabolism and to be highly prevalent (58% to 86%) among obese type 2 diabetics.

**Objective:** To determine the effect of untreated OSA on hemoglobin A₁c (HbA₁c) in type 2 diabetics.

**Participants/Methods:** This study included 60 patients with type 2 diabetes who were on a stable medication regimen for ≥3 months, were identified consecutively in primary care and endocrinology clinics without regard to sleep-related symptoms, had undergone nocturnal polysomnography (PSG), and had determination of HbA₁c. Five patients had been previously diagnosed with OSA but were not using treatment for that condition; use of nocturnal oxygen or treatment for OSA was among the exclusion criteria.

**Results:** Body mass index (BMI) ranged from 20 to 57 kg/m². By PSG, 77% of patients (46 of 60) had OSA, which was mild in 38%, moderate in 25%, and severe in 13%. Those with OSA were heavier (average BMI, 35 vs 29), were 6 years older on average, and had more complications of diabetes than those without OSA (65% of those with OSA had complications vs 21% of those without OSA). After controlling for a number of factors including age and BMI, researchers found that HbA₁c still correlated with OSA severity. Compared to those without OSA, HbA₁c was 1.5 points higher in those with mild OSA, 1.9 points higher in those with moderate OSA, and 3.7 points higher in those with severe OSA. This correlation also held with other measures of OSA severity, including oxygen desaturation index.

**Conclusions:** This study demonstrated “for the first time a clear, graded, inverse relationship between OSA severity and glucose control in patients with type 2 diabetes,” with an effect size similar to that of commonly used diabetes medications. Researchers advise systematic evaluation and treatment of OSA in type 2 diabetics, and advise against treatments for diabetes, which lead to weight gain.

**Reviewer’s Comments:** This study did not determine causality or direction of effect in the HbA₁c-OSA relationship, nor did it evaluate whether treatment for OSA improves HbA₁c. Unfortunately, treatments for OSA are often unappealing or unpleasant for patients to use. Weight loss, although difficult, can clearly improve glucose control as well as OSA severity in overweight and obese subjects and is the best long-term approach, when it can be achieved. Physicians should keep a high index of suspicion for OSA in patients with type 2 diabetes and pursue diagnostic testing in patients who might act on an OSA diagnosis, even if by “only” redoubling their efforts at weight loss. (Reviewer-Eliza L. Sutton, MD).

© 2010, Oakstone Medical Publishing

Keywords: Obstructive Sleep Apnea, Type 2 Diabetes Mellitus

Print Tag: Refer to original journal article
Long-term bisphosphonate therapy may increase the risk of odd fractures, especially long-bone mid-shaft fractures.

**Background:** Bisphosphonates have been in use for about 20 years. They have been effective in decreasing the risk of typical osteoporotic fractures. Because of the unusually long half-life in bone of these medications, there is concern that long-term use could lead to oversuppression of bone turnover, compromising bone quality and bone strength. Case reports of mid-shaft fractures in patients on bisphosphonates have further raised this concern.

**Objective:** To present the clinical presentation and x-ray images of patients with mid-shaft fractures on bisphosphonate therapy.

**Methods:** This is a case series involving 13 patients, 6 diagnosed at the University of Texas Southwestern Medical Center and 7 diagnosed at Henry Ford Hospital in Detroit. All 13 patients were on long-term bisphosphonates (10 on alendronate and 3 on risedronate) and sustained nontraumatic mid-shaft fractures occurring during normal activities of daily living.

**Results:** Of 13 patients who sustained mid-shaft fractures while on bisphosphonates, 9 of 10 taking alendronate had been on the drug for >5 years. Eleven of 13 patients sustained mid-shaft femur fractures. Six patients underwent bone biopsy; in 5 of these patients, there was evidence of severe suppression of bone turnover.

**Conclusions:** Long-term bisphosphonate therapy may increase the risk of long-bone mid-shaft fractures.

**Reviewer's Comments:** This is another case series that points out the occurrence of unusual mid-shaft fractures of long bones in patients receiving long-term bisphosphonates. This still appears to be a rare occurrence, but it is a severe complication when it occurs. It further raises the question of how long patients should receive bisphosphonates. Current suggestions include limiting bisphosphonate use to 5 years unless patients have had recurrent vertebral fractures. (Reviewer-Douglas S. Paauw, MD.)

© 2010, Oakstone Medical Publishing

Keywords: Osteoporosis, Bisphosphonate Therapy, Mid-Shaft Fractures

Print Tag: Refer to original journal article
Higher levels of physical activity among men with nonmetastatic colorectal cancer are associated with improved colorectal cancer-specific and overall survival.

**Background:** Observational studies have found that being physically active lowers the risk of developing colorectal cancer; however, it is not known if exercise is associated with improved mortality among colorectal cancer survivors.

**Objective:** To evaluate the association between physical activity and colorectal cancer mortality.

**Design:** Prospective cohort study.

**Participants/Methods:** The study subjects were 668 men with a history of stage I to stage III colorectal cancer diagnosed between 1986 and 2004 who were enrolled in the Health Professionals Follow-up Study. Physical activity was assessed from biennial questionnaires, and metabolic equivalent task (MET) scores in hours per week were determined and categorized as follows: <3; 3.1 to 9; 9.1 to 18; 18.1 to 27; or >27. Men who died within 6 months of their post-diagnosis physical activity assessment were excluded to minimize bias introduced by occult recurrences or other undiagnosed illnesses. Hazard ratios (HR) were calculated and adjusted for potentially confounding variables.

**Results:** Of the 258 deaths, 88 were due to colorectal cancer; 50.4% of participants exercised at least 18 MET hours per week. Increasing physical activity levels were positively associated with improved colorectal cancer-specific survival and overall survival ($P = 0.002$ and $P < 0.001$ for trend, respectively). The adjusted HR for colorectal cancer-specific mortality for men who exercised >27 MET hours/week (38.1% of participants) compared to those who exercised <3 MET hours/week (15.4% of participants) was 0.47 (95% CI, 0.24 to 0.92). For overall mortality, the adjusted HR was 0.59 (95% CI, 0.41 to 0.86). Since recent diagnosis or treatment of colorectal cancer could result in decreased physical activity levels, the analyses were repeated excluding participants who died within 6, 12, or 24 months of completing the physical activity assessment; for each of these analyses, the results were unchanged.

**Conclusions:** In this cohort of men with nonmetastatic colorectal cancer, “more physical activity was associated with a lower risk of colorectal cancer-specific and overall mortality.”

**Reviewer’s Comments:** Higher levels of physical activity among men with nonmetastatic colorectal cancer were associated with improved colorectal cancer-specific and overall survival. The most active men were half as likely to die of colorectal cancer as the least active men. This association persisted regardless of age, disease stage, body mass index, year of diagnosis, tumor location, and pre-diagnosis physical activity level. The mechanism is unknown but may be related to exercise-induced metabolic alterations, which inhibit the growth of micrometastases present at the time of diagnosis. The results of this study support the potential role of exercise as a powerful means to decrease the risk of death among colorectal cancer survivors. The authors note that a randomized trial of stage II and III colorectal cancer survivors (comparing those who receive general educational materials with those involved in a supervised physical activity program) will soon begin enrolling patients. In the mean time, patients with colorectal cancer should be advised to exercise. (Reviewer-Elaine F. Sachter, MD).

© 2010, Oakstone Medical Publishing

Keywords: Colorectal Cancer, Survival, Physical Activity

Print Tag: Refer to original journal article

The ACOG recommends that cervical cancer screening may be done at intervals >3 years in low-risk women aged ≥30 years who have normal cytologic results and who test negative for high-risk human papillomavirus strains.

**Background:** The incidence of cervical cancer has declined in the United States due to widespread screening. Changes in technology and advances in knowledge about human papillomavirus (HPV) as the causative agent, including the natural history of HPV infection and cervical dysplasia, necessitate periodic review and update of screening recommendations.

**Objective:** To review the evidence on cervical cancer screening techniques and on benefits and harms of screening to conclude with evidence-based, updated recommendations for screening. **Level A Recommendations:** These were based on good and consistent scientific evidence. (1) Both liquid-based and slide-based collection techniques are acceptable. (2) Screening should begin at age 21 years, not earlier, to avoid potentially harmful and unnecessary procedures on the cervix in younger women. (3) Screening should be performed every 2 years for women aged 21 to 29 years. (4) Screening may be extended in low-risk women aged ≥30 years as follows: (a) every 3 years after 3 consecutive normal cytologic screenings, or (b) "no sooner than 3 years" after negative co-screening by cytology and for high-risk HPV. (Co-screening every 6 years performed better than cytology alone every 3 years in studies on screening strategies.) Low-risk means no history of cervical intraepithelial neoplasia 2 (CIN-2) or CIN-3, no immunocompromise including HIV, and no history of diethylstilbestrol exposure in utero. (5) Screening should be discontinued in women who have undergone hysterectomy with removal of the cervix for benign indications and who have no history of high-grade CIN. **Level B Recommendations:** These were based on limited and inconsistent scientific evidence. (1) Annual screening should continue for 20 years after CIN-2, CIN-3, or cervical cancer, and potentially even longer after hysterectomy with this history. (2) "It is reasonable to discontinue" screening between age 65 to 70 years in women who have had no abnormal tests in the previous 10 years and who have had at least 3 negative results in a row. **Level C Recommendations:** These were based on consensus or expert opinion. (1) Vaccination against HPV strains 16 and 18 should not change cervical cancer screening guidelines. (2) "Annual gynecologic examinations may still be appropriate even if cervical cytology is not performed at every visit."

**Reviewer's Comments:** Specialty group guidelines for cancer screening are frequently more aggressive than guidelines by generalist groups. With this update, however, the American College of Obstetricians and Gynecologists has used evidence about the natural history of HPV infection and cervical cytologic abnormalities in recommending that screening not begin before age 21 and should be performed less often in low-risk women. (Reviewer-Eliza L. Sutton, MD).

© 2010, Oakstone Medical Publishing

Keywords: Cervical Cancer, Guidelines

Print Tag: Refer to original journal article
Expectations About Sleep Differ by Type of Insomnia

Examining Maladaptive Beliefs About Sleep Across Insomnia Patient Groups.

Carney CE, Edinger JD, et al:

J Psychosom Res 2010; 68 (January): 57-65

People with difficult-to-treat insomnia and/or those on long-term sleep medications may benefit from cognitive restructuring and sleep education as part of cognitive behavioral treatment for insomnia.

**Background:** Unrealistic expectations about sleep can perpetuate insomnia. On the 16-item Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS-16), respondents score statements about sleep (0 = completely disagree, 10 = completely agree). Elevated scores indicate that cognitive restructuring and sleep education, 2 aspects of cognitive behavioral therapy for insomnia (CBTI), may be effective.

**Objective:** To compare DBAS-16 scores in good sleepers and people with insomnia of different types.

**Design:** Archival study of data previously collected at 5 sites in the United States, Canada, and Australia.

**Participants:** 335 "good sleepers" (GS) and 1049 people with insomnia (PWI) who fell into 1 of 4 groups (primary insomnia, long-term hypnotic users, insomnia attributed to medical conditions, and insomniacs referred to tertiary center sleep clinics). Ages ranged from 18 to 89 years, with an average age 30 years for GS, 44 years for those referred to sleep clinics, 63 years for hypnotic users, and 69 years for those with medical conditions causing insomnia.

**Results:** The mean score on the DBAS-16 was 2.96 for GS, 4.27 for people with medical conditions causing insomnia, 4.38 for those with primary insomnia, 5.14 for long-term hypnotic users, and 6.16 for those referred to sleep clinics from the community. Average scores differed most between GS and PWI for these 3 statements: "I am worried that I may lose control over my ability to sleep" (1.65 for GS vs 5.02 for PWI); "Insomnia is ruining my life" (2.43 vs 5.23); and "I can't ever predict whether I will have a good or poor night" (4.23 vs 7.00). Average scores differed least between GS and PWI for "I think insomnia is due to a chemical imbalance," "Need to catch up on sleep loss," and "I need 8 hours of sleep to function." A cut-off score of 3.8 maximized sensitivity and specificity of the DBAS-16 for detecting insomnia at 80% and 76%, respectively.

**Conclusions:** Insomniacs referred from the community to sleep clinics (at tertiary care centers) and people who used long-term hypnotic medications had the most dysfunctional beliefs about sleep. Cognitive treatments can help.

**Reviewer's Comments:** In this study, 2 groups well known to general internists had the highest average scores on the DBAS-16: people treated long term with hypnotics, and those referred to sleep specialists for insomnia. People with medical conditions causing their insomnia had relatively low scores. The greatest differences with good sleepers were in the sense of loss of control over sleep, which, ironically, heightens vigilance and perpetuates insomnia. (Reviewer-Eliza L. Sutton, MD).

© 2010, Oakstone Medical Publishing

Keywords: Insomnia, Maladaptive Beliefs

Print Tag: Refer to original journal article
Antidepressant medication efficacy over placebo increases with increasing severity of depression symptoms.

**Background:** It is common practice to use antidepressants in the treatment of both mild and moderate depressive symptoms. However, the majority of efficacy data for antidepressants have been shown in trials that included only severely depressed patients.

**Design:** Patient-level meta-analysis of randomized, controlled trials.

**Participants:** Adult ambulatory care patients with depression.

**Methods:** A meta-analysis of randomized, controlled trials was performed in standard fashion. Inclusion criteria were FDA-approved antidepressants, used to treat the full range of depression severity as measured by the Hamilton Depression Rating Scale (HDRS), compared to placebo. The trial duration was ≥6 weeks, and individual data were available for analysis. Exclusions were special populations or specific depression subtypes, studies consisting exclusively of dysthymic patients, and the use of a placebo washout period. Six trials were included, 3 using paroxetine and 3 with imipramine. Data were analyzed for 718 patients. Minimal intake depression severity ranged from mild to severe.

**Results:** The data were pooled, and the difference between the treatment effect size of the antidepressant and the placebo (Cohen d effect size) were analyzed based on the initial depression severity score. For mild-moderate depression, $d = 0.11$ (CI, $-0.18$ to $0.41$; number needed to treat [NNT], 16); for severe depression, $d = 0.17$ (CI, $-0.08$ to $0.43$; NNT, 11); and for very severe depression, $d = 0.47$ (CI, $0.22$ to $0.71$; NNT, 4). The authors considered $d = 0.20$ to be a minimal effect and $d = 0.50$ to be a moderate effect size; this also represented the cut-off for clinical significance or a 3-point difference in HDRS scores. Antidepressant medications were more effective than placebo with a moderate effect size if the patient's HDRS score was 25; medications were superior to placebo with a large effect if the HDRS score was ≥27.

**Conclusions:** The efficacy of antidepressant medication therapy varied as a function of depression severity, with lack of efficacy in antidepressant medication over placebo for mild and moderate depression.

**Reviewer's Comments:** This article supports the conclusions of 2 previous meta-analyses showing that antidepressant medication efficacy over placebo increased with increasing depression severity. It is unclear if antidepressants perform better in those with very severe depression or if placebo performs worse. Placebo has a strong effect in patients with depression, and the authors purposefully excluded trials with a placebo washout period that selected out patients with a robust placebo response. Physicians should reconsider the use of antidepressant medications as primary therapy for those with mild and moderate severity depressive symptoms. However, since the majority of efficacy trials for depression have included only patients with severe depression, more trials of mild to moderate depression should be conducted. (Reviewer-Genevieve L. Pagalilauan, MD).

© 2010, Oakstone Medical Publishing

Keywords: Antidepressants, Depression Severity, Treatment

Print Tag: Refer to original journal article
Higher Risk of Stroke, Death in Women on Antidepressants

Antidepressant Use and Risk of Incident Cardiovascular Morbidity and Mortality Among Postmenopausal Women in the Women's Health Initiative Study.
Smoller JW, Allison M, et al:

Arch Intern Med 2009; 169 (December 14/28): 2128-2139

Diagnosis with depression correlates with higher subsequent risk of morbidity and mortality; antidepressant use may not mitigate that risk, or may pose its own risk.

**Background:** Antidepressants (ADs) are widely prescribed. Depression has been associated with increased risk of coronary heart disease (CHD) morbidity and mortality, and ADs may affect the risk of cardiovascular events.

**Objective:** To examine the association between CHD, stroke, and mortality with AD use.

**Design:** Prospective observational study.

**Participants/Methods:** 136,923 women enrolled in the Women's Health Initiative who were not taking ADs at enrollment and who presented for at least one follow-up visit. Of these women, 5496 were taking an AD at first follow-up and were observed for cardiovascular events and mortality (average, 5.9 years).

**Results:** 22% of those who later started ADs initially met criteria for depression (vs 8% of non-AD users). Women who began an AD were younger and were more likely to be taking hormones, to report migraines, to take aspirin or anti-inflammatory medications, to take medication for hyperlipidemia and/or diabetes and/or hypertension, to have a history of heart disease and/or stroke, to be sedentary, to be a current or past smoker, to be a past drinker, to be from the South, to be white, and to have a regular health care provider. They also had more "life events" in the past year. The researchers adjusted for these differences. AD use was not associated with increased CHD risk but was associated with increased risk of stroke and all-cause mortality. Risk from selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants were similar overall, including a 2-fold higher risk of fatal stroke; SSRIs increased the risk of hemorrhagic stroke 2-fold.

**Conclusions:** This was the largest study to date examining the effects of AD therapy on health. The researchers concluded that the effect of AD treatment could be from the residual effect of depression, rather than from the medication(s). They also concluded that, at minimum, the treatment of depression does not mitigate the effect of depression on mortality risk, and that attention should be paid to a reduction in cardiovascular risks in postmenopausal women treated for depression.

**Reviewer's Comments:** While antidepressant use at first follow-up may have been prescribed most often for depression, there are other possible reasons for AD use. The women who reported starting ADs were in worse health than women who did not. This observational study used only one time point to determine classification of participants as AD users versus non-users, but health outcomes were followed over nearly 6 years. My conclusion is this: among postmenopausal women, having an indication for antidepressant prescription correlates with higher subsequent risk of stroke and all-cause mortality. (Reviewer-Eliza L. Sutton, MD).

© 2010, Oakstone Medical Publishing

Keywords: Antidepressants, Cardiovascular Events, Morbidity, Mortality, Postmenopause

Print Tag: Refer to original journal article
How Should FMH Be Used?

Berg AO, Baird MA, et al:

Ann Intern Med 2009; 151 (December 15): 872-877

The family medical history is specific but not sensitive for determining the risk for most common medical conditions in the primary care setting.

**Background:** Despite pervasive use, little has been studied about the useful components, administration, and benefits and harms of obtaining a family medical history (FMH).

**Objective:** To evaluate the use of the FMH for common diseases seen in primary care.

**Design:** National Institutes of Health (NIH) consensus statement based on the Wilson et al systematic review in the same issue of *Annals of Internal Medicine* (December 15, 2009).

**Participants:** Primary care patients.

**Methods:** Outcomes of interest were key FMH elements for assessing the risk of common medical problems, accuracy, evidence of health benefits and harms, and factors on obtaining and using the FMH. The common medical conditions evaluated were asthma and allergy, diabetes, major depression and mood disorder, cardiovascular disease, and cancer (breast, ovarian, colorectal, prostate, and lung).

**Results:** 59 longitudinal or cross-sectional studies were included. Asking about the FMH of a specific condition and asking about a condition in a first-degree relative were commonly assessed. Distinguishing maternal versus paternal history, gender of affected relative, and age of onset had little supporting evidence. The sensitivity was <25% and the positive-predictive value (PPV) was <10%, but specificity ranged between 90% and 98%. Exceptions were atopic dermatitis, mood disorders, and depression, which had a sensitivity of approximately 50% and a specificity of 50% to 75%. Subjects were accurate for identifying negative FMH (specificity, 90% to 95%) but not positive FMH (sensitivity, 33% to 95% for cancer and 6% to 82% for mental health conditions). No studies reported morbidity or mortality directly, but 2 trials showed increased rates of self-breast exam and clinical breast exam 6 months after FMH was obtained. Three studies showed a modest short-term increase in anxiety in patients with FMH that conferred an increased risk.

**Conclusions:** The FMH may have a role in motivating positive lifestyle changes and influencing clinical interventions, but it is unclear how to obtain and use this information. There is weak evidence to support obtaining FMH for common diseases in primary care settings, and further studies are encouraged.

**Reviewer’s Comments:** Research is needed on this topic. FMH is far more specific than sensitive, but values vary with disease prevalence and genetic penetration. Better clarification of the strength of the association of common conditions and FMH might help target our efforts. People are more accurate in reporting a negative FMH, so we must be wary of the risk of changing screening or treatment plans based on a false-positive FMH. This article also highlights how FMH accuracy may suffer from limitations in health literacy, and underscores that we must be mindful of under-reporting on health conditions with a negative social bias. (Reviewer-Genevieve L. Pagalilauan, MD).

© 2010, Oakstone Medical Publishing

Keywords: Common Medical Conditions, Family Medical History, Risk Assessment

Print Tag: Refer to original journal article