

## ACEI Plus Second Agent for Hypertension -- Amlodipine or Hydrochlorothiazide?

*Cardiovascular Events During Differing Hypertension Therapies in Patients With Diabetes.*

Weber MA, Bakris GL, et al:

J Am Coll Cardiol 2010; 56 (June 29): 77-85

In combination with an ACE inhibitor, the use of amlodipine is superior to hydrochlorothiazide in preventing cardiovascular events in diabetics with hypertension.

**Background:** Many patients with hypertension need more than one drug to control their blood pressure. Angiotensin-converting enzyme inhibitors (ACEIs) are commonly used. The most commonly added drugs to ACEIs are thiazide diuretics. This combination is effective at controlling blood pressure and is an inexpensive option. The Avoiding Cardiovascular Events Through COMBination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial was performed to compare an ACEI (benazepril) with hydrochlorothiazide with a benazepril/amlodipine combination.

**Objective:** To evaluate data from the ACCOMPLISH trial, specifically the subgroup of diabetic patients.

**Methods:** A prespecified analysis of the ACCOMPLISH trial was an analysis of outcomes in diabetic patients. A total of 6946 patients with diabetes and hypertension were randomized to receive benazepril plus hydrochlorothiazide or benazepril plus amlodipine. The primary end point was a composite of vascular complications (cardiovascular death, hospitalization for angina, resuscitated cardiac arrest, myocardial infarction, cardiac revascularization, and stroke).

**Results:** The mean blood pressures were not significantly different (131.5/72.6 mm Hg for those receiving benazepril/amlodipine and 132.7/73.7 mm Hg for those receiving benazepril/hydrochlorothiazide). Primary end points were fewer in patients who received amlodipine, 8.8% versus 11% for those receiving hydrochlorothiazide (HR, 0.79; CI, 0.68 to 0.92;  $P=0.003$ ). In a subgroup of diabetic patients at very high risk, there were even more significant differences, 13.6% for those treated with an amlodipine regimen versus 17.3% on the diuretic regimen (HR, 0.77;  $P=0.007$ ).

**Conclusions:** The combination of benazepril/amlodipine was better in reducing cardiovascular end points than benazepril/hydrochlorothiazide in diabetic patients.

**Reviewer's Comments:** This study looks as if amlodipine combined with benazepril is better than the standard of combining it with hydrochlorothiazide. The results were significant, favoring amlodipine. I am concerned about what was measured, however. The primary end point was a composite of multiple cardiovascular outcomes, including hospitalization for angina. There was no significant difference between the regimens in fatal and non-fatal myocardial infarction, hospitalization for unstable angina, stroke, cardiovascular death, or all-cause death. Interestingly, there was a very significant ( $P<0.001$ ) difference in renal outcomes, favoring the amlodipine group. The number needed to treat for the primary composite end point was 45. The group receiving amlodipine had significantly more side effects (one third of these patients had peripheral edema). (Reviewer-Douglas S. Paauw, MD).

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Keywords: Hypertension, ACE Inhibitors, Diabetes

Print Tag: Refer to original journal article

## Reducing BP With CPAP -- Nothing to Yawn About

*Continuous Positive Airway Pressure Treatment in Sleep Apnea Patients With Resistant Hypertension: A Randomized, Controlled Trial.*

Lozano L, Tovar JL, et al:

J Hypertens 2010; 28 (June 23): epub ahead of print

In patients requiring 3 to 5 antihypertensive medications, evaluation for obstructive sleep apnea and subsequent treatment with CPAP therapy may help reduce 24-hour blood pressure and restore nocturnal dipping.

**Background:** One third of U.S. adults have hypertension, which is inadequately controlled in approximately 50%. Obstructive sleep apnea (OSA) is associated with hypertension (and other cardiovascular disease). Continuous positive airway pressure (CPAP) has shown a small effect in reducing blood pressure in people with severe OSA but has little to no effect in those with milder OSA.

**Objective:** To examine the effect of CPAP therapy in people with resistant hypertension and OSA.

**Participants/Methods:** The study involved hypertension clinic patients taking 3 to 5 antihypertensive medications but with elevated blood pressures (>140/90 mm Hg in clinic or >125/80 mm Hg on 24-hour monitoring; n=96). Patients had an apnea-hypopnea index >15 on polysomnography (n=75) and were randomized to either CPAP therapy or to usual treatment for 3 months; 24-hour ambulatory blood pressure monitoring was performed at the start and end of the study.

**Results:** 64 patients completed the study (9 in the CPAP arm either refused to try CPAP or were unable to tolerate it; 2 were lost in the usual treatment arm). Median CPAP use was 5.8 hours a night. After 3 months, those with 24-hour resistant hypertension (rather than in-clinic elevated readings only) who used CPAP for >5.8 hours/night showed a reduction in 24-hour systolic (-9.7 mm Hg) and diastolic (-7.0 mm Hg) blood pressures and in daytime diastolic blood pressure (-6.1 mm Hg). Nocturnal dipping of blood pressure was present in 50% of the CPAP group at baseline and in 76% at study end; there was no change in the usual treatment arm.

**Conclusions:** In patients with resistant hypertension and OSA who are able to tolerate nocturnal CPAP therapy, treatment for >5.8 hours a night for 3 months reduces 24-hour systolic and diastolic blood pressures and daytime diastolic blood pressure. It also restores nocturnal dipping in half of nondippers.

**Reviewer's Comments:** Seventy-eight percent of these patients on 3 to 5 blood pressure medications had OSA (similar to at least one prior study), and 76% of those randomized to CPAP were able to use it. Half the patients used CPAP for >5.8 hours a night (the group's median use and the level above which a statistically significant benefit was seen). Therefore, perhaps up to 30% of patients with resistant hypertension could potentially benefit (blood pressure wise) from evaluation and treatment for OSA. The absolute decrease in daytime blood pressure with nocturnal CPAP is modest, but restoration of normal dipping during sleep and a mean decrease in blood pressure over 24 hours by almost 10 mm Hg systolic and 7 mm Hg diastolic are nothing to yawn about. (Reviewer-Eliza L. Sutton, MD).

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Keywords: Hypertension, OSA, Continuous Positive Airway Pressure

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## Is Rituximab Effective for Wegener's and AAV?

*Rituximab Versus Cyclophosphamide for ANCA-Associated Vasculitis.*

Stone JH, Merkel PA, et al:

N Engl J Med 2010; 363 (July 15): 221-232

Rituximab is as effective as cyclophosphamide for induction of remission and is superior to cyclophosphamide for the treatment of relapse in antineutrophil cytoplasmic antibody-associated vasculitis.

**Objective:** To provide a head-to-head comparison of rituximab and cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

**Participants/Methods:** 197 ANCA-positive patients with either Wegener's or microscopic polyangiitis were randomized to receive remission induction with either rituximab (R; 99 patients) or cyclophosphamide (C; 98 patients). The R protocol was 375 mg/m<sup>2</sup> given IV weekly for 4 doses over 4 weeks. The C protocol required 2 mg/kg cyclophosphamide given orally daily. Both groups of patients received methylprednisolone 1 g IV for 1 to 3 pulses at onset followed by oral prednisone 1 mg/kg per day. A tapering schedule of prednisone dosing allowed patients in remission to discontinue prednisone at 5 months.

**Results:** 64% of R-treated patients achieved remission off prednisone at 6 months compared to 53% of C-treated patients. This difference achieves noninferiority by definition. When patients with relapsing disease were evaluated, 67% of R-treated patients with relapse reached the primary end point (no active disease and off prednisone at 6 months) compared to 42% in the C-treated group; this difference was highly statistically significant with  $P=0.01$ . There was a tendency for the Wegener's patients to respond to R better than the microscopic polyangiitis patients, but this trend did not reach statistical significance. Wegener's patients are often PR-3 antibody positive, and this test converted to negative more often with R treatment than with C treatment (50% vs 17%). The anti-MPO antibody positive patients were equally responsive to both treatments with a rate of conversion from antibody positive to antibody negative of 40% for R and 41% for C-treated groups.

**Conclusions:** Despite theorizing that the presence of ANC antibody is directly toxic to endothelial cells and thus a direct cause of disease manifestations, there was no correlation between the ability of each treatment regimen to convert the antibody tests to negative with achieving remission.

**Reviewer's Comments:** Rituximab did well at inducing remission and treating relapse in this group of 197 patients with AAV. In the subgroup of patients with severe renal disease or alveolar hemorrhage, the response rates were similar in both treatment (R) and control (C) groups. This observation corroborates the findings from the rituximab in AAV with renal disease paper in the same issue of the *New England Journal of Medicine*. Longer-term observation of this cohort could help determine which treatment is best at maintaining remission without relapse, and whether repeated dosing of rituximab and/or adding a maintenance therapy after R is given would improve outcomes. (Reviewer-Peggy Schlesinger, MD).

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Keywords: ANCA-Associated Vasculitis, Rituximab, Cyclophosphamide

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## Rituximab vs Cyclophosphamide in ANCA-Associated Vasculitis With Renal Disease

*Rituximab Versus Cyclophosphamide in ANCA-Associated Renal Vasculitis.*

Jones RB, Tervaert JWC, et al:

N Engl J Med 2010; 363 (July 15): 211-220

Both rituximab and cyclophosphamide are effective in the induction of remission in severe antineutrophil cytoplasmic antibody-associated vasculitis with renal disease.

**Background:** This long-awaited article outlining the results of the rituximab versus cyclophosphamide in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (RITUXVAS) trial of ANCA associated vasculitis (AAV) with significant renal involvement has interesting results. The hope has been that the use of rituximab early in the course of AAV would lead to less morbidity and fewer relapses compared to standard induction protocols using cyclophosphamide, and to the transition to azathioprine for maintenance therapy.

**Objective:** To report on the outcomes of AAV after rituximab induction of remission compared with standard cyclophosphamide induction.

**Participants/Methods:** 44 patients were randomized, 33 to the rituximab group and 11 to the cyclophosphamide group. Both groups received IV methylprednisolone up to 2 g and/or plasma exchange initially before randomization due to the severity of disease. Significant renal disease was documented at onset with necrotizing glomerulonephritis on renal biopsy and abnormal active urine sediment. Primary outcomes were sustained remission and rates of severe adverse events at 12 months. The rituximab induction protocol included rituximab 375 mg/m<sup>2</sup> IV once a week for 4 weeks total with 2 cyclophosphamide (15 mg/kg per dose) IV infusions given at week 1 and 3 with the rituximab infusion. A third cyclophosphamide infusion could be given if relapse occurred within the first 6 months. The cyclophosphamide induction protocol included cyclophosphamide given IV once a month for 3 to 6 months at 15 mg/kg per dose followed by maintenance oral azathioprine therapy. Both groups received methylprednisolone IV 1 g initially after randomization followed by oral prednisone at 1 mg/kg, with tapering of the dose down to 5 mg/day at the end of 6 months.

**Reviewer's Comments:** Ninety-one percent of surviving patients in each group achieved sustained remission at 6 months. The majority of deaths occurred in the first 3 months of treatment, and the 18% death rate was the same in both groups. The relapse rate at 12 months was 15% in the rituximab group and 10% in the cyclophosphamide group, which was not a statistically significant difference. This study shows rituximab induction to be as effective but not more effective than cyclophosphamide standard therapy for severe AAV with renal disease. (Reviewer-Peggy Schlesinger, MD).

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Keywords: Rituximab, ANCA, Vasculitis, Renal Disease

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## Glucosamine Disappointing for LBP From Osteoarthritis

*Effect of Glucosamine on Pain-Related Disability in Patients With Chronic Low Back Pain and Degenerative Lumbar Osteoarthritis: A Randomized Controlled Trial.*

Wilkens P, School IB, et al:

JAMA 2010; 304 (July 7): 45-52

Despite wide use, glucosamine does not improve pain-related disability in patients with lumbar osteoarthritis.

**Background:** Glucosamine, with or without chondroitin, has been tried in osteoarthritis (OA) patients in several studies without clear and convincing beneficial effect on pain. Glucosamine is thought to benefit OA patients by providing large quantities of precursor used in building cartilage to those who have little cartilage left. However, lack of standardized preparations and design differences have made results of these prior trials less than convincing, with only a mild effect on pain in knee and hip OA seen on meta-analysis.

**Objective/Methods:** In this well-controlled trial from Norway, 250 people with lumbar OA and chronic low back pain (LBP) were randomized to treatment with either placebo or 1.5 g of glucosamine sulfate (GS) daily. Lumbar OA was documented on MRI with evidence of degeneration present at disc and/or facet joints. The GS preparation was standardized and could be taken in either once-daily or split-dosing regimens. Very few side effects were noted in both treatment and placebo groups, demonstrating that GS is generally well tolerated. Patients in both groups were allowed to use their usual medication and rescue pain medications, plus ongoing physical therapy and massage. Patients were evaluated at 6 weeks, 12 weeks, 6 months, and by mail-in questionnaire at 1 year, using a validated measure of pain-related disability, a pain scale, and a quality-of-life instrument.

**Results/Conclusions:** The results assessed at 6 months and 1 year showed no significant benefit of GS treatment over placebo in reducing pain-related disability from lumbar osteoarthritis.

**Reviewer's Comments:** This well-designed negative study adds to the practical approach to treating patients with LBP and disability. The accompanying editorial in the same issue by Dr Andrew Avins is excellent, pointing out the gap between the huge public health burden of LBP with resultant disability, and the paltry sums of research money allocated to finding effective treatment approaches to this common problem. All of us who treat these patients welcome well-done studies that can channel our therapeutic efforts toward treatments that are likely to be effective. This negative study is very helpful in that regard. (Reviewer-Peggy Schlesinger, MD).

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Keywords: Low Back Pain, Osteoarthritis, Glucosamine

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## Corticosteroids, PT, or Both for Shoulder Pain?

*Exercise Therapy After Corticosteroid Injection for Moderate to Severe Shoulder Pain: Large Pragmatic Randomised Trial.*

Crawshaw DP, Helliwell PS, et al:

BMJ 2010; 340 (June 28): c3037

Consider subacromial steroid injection in addition to PT in patients with moderate to severe impingement shoulder symptoms who prioritize early improvement in pain and function.

**Background:** "Use it or lose it" is the advice we give patients with severe shoulder pain. In hopes of improving their ability to participate in physical therapy (PT), physicians perform corticosteroid injections.

**Objective:** To compare subacromial corticosteroid injection plus exercise and manual therapy (steroid plus PT) versus exercise and manual therapy alone (PT alone) for the end points of shoulder pain and disability.

**Design:** Randomized clinical trial.

**Methods:** Subjects aged  $\geq 40$  years with unilateral moderate to severe shoulder pain, impingement symptoms, and "noncapsular restriction" were identified. All subjects were taught pendulum exercises. The steroid plus PT patients had 20 mg of triamcinolone and 4.5 cc of 1% lidocaine injected by a specially certified physical therapist, and then started PT 1 week later. The PT-only patients started PT immediately. The number of PT sessions was determined individually at the discretion of the physical therapist. The shoulder pain and disability index (SPADI), which measured scores from 0 to 100 (with 100 being severe pain and disability) was obtained at 1, 6, 12, and 24 weeks. The primary outcomes of interest were total score and subset score of pain and function at 12 weeks.

**Results:** 115 patients were randomized to the injection plus PT arm, and 117 to the PT-only arm. There was no difference in the mean disability and pain score at 12 weeks between the 2 arms. The change in the SPADI score (from baseline to week 12) for PT only was -23.6, and for steroids plus PT was -28.5 ( $P=0.111$ ). The difference in 12-week scores between arms was 4.9 (CI, -1.1 to 11). Improvement was better at weeks 1 and 6 for the injection plus PT arm compared to PT alone, with the difference between arms being 6.6 (CI, 4.3 to 8.8) and 7.37 (CI, 4.3 to 10.4), respectively. At 24 weeks, there was no statistical difference in pain and function between arms.

**Conclusions:** In patients with moderate to severe shoulder pain due to impingement syndrome, corticosteroid injection plus exercise and manual therapy is similarly effective to exercise and manual therapy alone.

**Reviewer's Comments:** Overall, this pragmatic study is well done. There was no blinding to the intervention, so there may be a placebo effect in the steroid plus PT arm. What I take away from this study is that corticosteroid injection helps with early pain and function but makes no difference in longer-term outcomes compared to PT alone. It seems reasonable to offer corticosteroid injections and leave it to patient preference. Although there was no difference in outcomes at 12 weeks, patients who opt for PT alone should be warned that one third of the PT-only group required additional therapy such as corticosteroid injections between 12 and 52 weeks of follow-up. (Reviewer-Genevieve L. Pagalilauan, MD).

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Keywords: Shoulder Pain, Corticosteroid Injection, Physical Therapy

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## Finnish Study Recommends Rituximab for RA Patients Who Fail TNFi

*Cost-Utility of Different Treatment Strategies After the Failure of Tumour Necrosis Factor Inhibitor in Rheumatoid Arthritis in the Finnish Setting.*

Hallinen TA, Soini EJO, et al:

Rheumatology 2010; 49 (April): 767-777

Rituximab with methotrexate is the most cost-effective treatment option in this Finnish computer modeling study of rheumatoid arthritis patients who have failed tumor necrosis factor inhibitor therapy.

**Background:** Rheumatoid arthritis (RA) patients are frequently started on biologic agents early in their disease course. However, if they fail to respond to treatment with a tumor necrosis factor inhibitor (TNFi), then what would be the next best course of action—continue with another TNFi or switch to a different biologic agent?

**Objective/Design:** This study from Finland used a computer modeling, cost-benefit analysis to evaluate which treatment option would be best in RA patients who had already failed to respond to one of the TNFi treatments. TNFi agents included etanercept, infliximab, and adalimumab.

**Methods:** The authors analyzed different treatment approaches that mirrored current medical practices in Finland to try to find the most efficacious, cost-effective next step after TNFi failure. Current Finnish practice is to begin treatment of RA patients with traditional disease-modifying anti-rheumatic drugs, beginning with a combination of sulfasalazine, methotrexate and hydroxychloroquine, then leflunomide and methotrexate, followed by either etanercept or adalimumab and methotrexate. If the patient with RA continues to have active disease after a trial of TNFi and methotrexate, the next step is not yet clearly identified. The computer modeling program considered all the treatment costs and associated costs plus quality of life gained, in a hypothetical RA patient who has been through this list of medication and continued to have active disease despite treatment with a combination of TNFi and methotrexate. Published response rates were used for each medication, and quality-of-life years were estimated based on disease severity scores for the approximately 3000 Finnish patients with RA. The patients in this computer model died at an average age of 75 years, approximately 5 years earlier than Finnish subjects without RA. An elevated risk multiplier was used for these hypothetical patients, mirroring the increased risk of death in real RA patients.

**Results/Conclusions:** Rituximab plus methotrexate is the most cost-effective choice of treatment in this computer model of RA patients resistant to treatment with one TNFi agent.

**Reviewer's Comments:** This is an interesting approach to identifying the best practice guidelines at different points in the treatment life of a hypothetical RA patient. The combination of government registry of diseases and treatments plus government control of drug costs helps model the options in this computer program. In Finland, one might do better with rituximab in patients who have failed one TNFi, whereas in the United States, we might forge ahead to use other drugs in the same class of TNFi before switching to a different biologic agent. Studies such as this one shed some light on making the choice of treatments based on cost effectiveness and improved quality of life. (Reviewer-Peggy Schlesinger, MD).

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Keywords: Rheumatoid Arthritis, Biologic Therapy

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## Is "Close" Good Enough for Corticosteroid Injections for Inflammatory Arthritis?

*A Randomized, Double-Blind, Controlled Study of Ultrasound-Guided Corticosteroid Injection Into the Joint of Patients With Inflammatory Arthritis.*

Cunnington J, Marshall N, et al:

Arthritis Rheum 2010; 62 (July): 1862-1869

Although ultrasound guidance improves the accuracy of joint injection, it does not improve short-term clinical outcome of the injections.

**Background:** Corticosteroid joint injections are commonly used for patients with inflammatory arthritis. Some patients have an outstanding clinical response, whereas others do not respond. The reason for the varied response is unknown, but lack of accuracy of the injection has been suspected as a possible cause.

**Objective:** To determine whether ultrasound guidance improves the accuracy and efficacy of corticosteroid injection of joints for inflammatory arthritis compared to injection by clinical exam alone.

**Methods:** The patients who participated in this study had inflammatory arthritis and were recruited from 4 outpatient rheumatology clinics in England. Patients were excluded if they required an immediate change of their treatment regimen. A total of 184 patients were randomized to receive either a joint injection of corticosteroids based on clinical exam (CE) alone or via ultrasound (US) guidance. Clinical response was assessed by several questionnaires completed by the patients at baseline, 2 weeks, and 6 weeks. In addition, erythrocyte sedimentation rate and C-reactive protein were measured at baseline and 2 weeks. Contrast was added to the injections to assess the exact location of the injection.

**Results:** Injections done by US guidance were more accurate than those done by clinical exam (83% vs 66%;  $P=0.01$ ). The knee was the most accurately injected joint (82%) based on clinical exam, and the shoulder was the least successful (40%) by clinical exam. No difference in inflammatory markers was found between groups, and no significant difference was seen in clinical outcome between the US and CE groups.

**Conclusions:** The use of ultrasound improves the accuracy of joint injection compared to clinical exam but does not change clinical outcome.

**Reviewer's Comments:** This article shows no difference in outcome when US is used to improve the accuracy of joint injections. Other studies have shown no benefit of US guidance for sacroiliac injections and trochanteric injections. A study published in the *Journal of Rheumatology* in 2009 showed a benefit of US-guided intra-articular injections, with a decrease in absolute pain scores by 58% at 2 weeks and a 26% increase in responder rate. The difference between the 2 studies was that the *Journal of Rheumatology* study used 2 syringes, with aspiration of fluid before injection of the steroid. This technique might further enhance the benefit of US. The current study used a single injection with contrast mixed in to determine if the injection was accurate. The accuracy rate was only 83% for US-guided injections in this study. (Reviewer-Douglas S. Paauw, MD).

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Keywords: Inflammatory Arthritis, Corticosteroid Injection, Ultrasound

Print Tag: Refer to original journal article



## Is PPI Risk to Bone Health Overstated?

*Proton Pump Inhibitor Use, Hip Fracture, and Change in Bone Mineral Density in Postmenopausal Women: Results From the Women's Health Initiative.*

Gray SL, LaCroix AZ, et al:

Arch Intern Med 2010; 170 (May 10): 765-771

Proton pump inhibitor use was associated with slightly more vertebral fractures but not hip fractures in the large Women's Health Initiative cohort.

**Background:** Over the past few years, several studies have been published suggesting that proton pump inhibitor (PPI) use is associated with osteoporosis and increased risk of hip fractures. The suspected mechanism has been decreased calcium absorption in patients taking PPIs.

**Objective:** To assess the risk of hip fracture and other fractures from PPI use in a large cohort of women.

**Methods:** This study was a prospective analysis of data from the Women's Health Initiative, with 161,806 postmenopausal women with no previous hip fracture enrolled. A total of 130,487 women were available for complete follow-up at a mean of 7.8 years. Medication use was assessed by direct observation of medication containers brought in by the participants at baseline and 3 years. Fractures were self reported by the participants, and a subgroup of the participants received bone density tests at baseline and 3 years.

**Results:** Current PPI users had a multivariate adjusted hazard ratio of 1.00 for hip fracture (CI, 0.71 to 1.40), 1.47 for vertebral fracture (CI, 1.18 to 1.82), 1.26 for forearm or wrist fracture (CI, 1.05 to 1.51), and 1.25 for total fracture (CI, 1.15 to 1.36). The use of PPIs was associated with decreased bone mineral density at the hip over 3 years compared to nonuse ( $P=0.05$ ).

**Conclusions:** PPI use was associated with small decreases in BMD at the hip and small increased fracture risks at the spine, wrist, and total fractures, but not hip fractures.

**Reviewer's Comments:** This study shows a slight association between PPIs and lower bone density. This was shown in lower bone density at the hip in a subgroup of patients who had bone density scans. There was a slight increased fracture risk. Unfortunately, the study did not look at the dose of PPIs that patients were taking. Other studies have found a dose response with fracture risk. Because many of the women were also on estrogen, overall bone density was frequently increased. Many patients ask about how dangerous PPIs are for their bones. The association is weak, but I believe it is real. If a patient needs a PPI, this problem should not stop the use but should remind us to use PPIs for as short a time as necessary. (Reviewer-Douglas S. Paauw, MD).

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Keywords: Osteoporosis, Proton Pump Inhibitors

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## Choose Brown Rice

*White Rice, Brown Rice, and Risk of Type 2 Diabetes in US Men and Women.*

Sun Q, Spiegelman D, et al:

Arch Intern Med 2010; 170 (June 14): 961-969

Brown rice intake is associated with reduced risk of diabetes mellitus.

**Background:** Brown rice has more fiber and nutrient value than white rice and may result in a lower risk of diabetes mellitus.

**Objective:** To compare the association of white and brown rice consumption with the risk of type 2 diabetes mellitus (DM2).

**Design/Methods:** Prospective assessment of diet, lifestyle, and active disease states among 39,765 men and 157,463 women in the Health Professionals Follow-up Study and the Nurses' Health Study.

**Results:** A higher intake of white rice (5 servings a week) was associated with a higher risk of DM2 compared with a lower intake (<1 serving a week), with a relative risk 1.17 (95% CI, 1.02 to 1.36). A higher intake of brown rice (2 servings a week) was associated with a lower risk of DM2 compared with a lower intake (<1 serving per month), with a relative risk of 0.89 (95% CI, 0.81 to 0.97). Adjustments were made for age, lifestyle, and other diet intake. The authors estimated that if one-third serving per day of white rice were routinely replaced with brown rice, this would result in a 16% lower risk of DM2 (95% CI, 9% to 21%), and replacing one-third serving per day of white rice with other whole grains would result in a 36% lower risk of DM2 (95% CI, 30% to 42%).

**Conclusions:** Substituting brown rice and other whole grains for white rice is associated with a lower risk of DM2, further supporting the intake of whole grains rather than refined grains.

**Reviewer's Comments:** Delicious and nutritious outer bran and germ layers of rice grains are removed in the refining process to create white rice, stripping rice of its many potential health benefits. More than 70% of the rice Americans consume is white rather than brown. This study begins by elucidating major differences between brown rice and white rice eaters at baseline. Heavy white rice eaters (compared to light white rice) were less likely to have European ancestry, were more likely to have a family history of diabetes, and were less likely to smoke. They also tended to eat more fruits/vegetables per week but reported a lower total intake of whole grains and cereals. Heavy brown rice consumers (compared with all other groups) tended to be more physically active, were less likely to smoke, and had a lower family history of diabetes. They also consumed more fruits, vegetables, and whole grains and consumed less red meat and trans fat. Detailed multivariate adjustment was undertaken for lifestyle and dietary factors, but I still wonder how much of the risk of diabetes is due to other subtle factors for which the authors were unable to adjust. Regardless, it is fairly easy to switch brown for white rice, and this study provides a compelling argument to do so. (Reviewer-Molly Blackley Jackson, MD).

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Keywords: Diabetes, Prevention

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## Low-Dose Transdermal Estradiol Does Not Increase Stroke Risk

*Transdermal and Oral Hormone Replacement Therapy and the Risk of Stroke: A Nested Case-Control Study.*

Renoux C, Dell'Aniello S, et al:

BMJ 2010; 340 (June 3): c2519

Transdermal estradiol doses up to 0.05 mg/day are not associated with increased stroke risk in postmenopausal women, in contrast to oral estrogens and to transdermal doses above 0.05 mg/day.

**Background:** Systemic estrogen use increases the risk of stroke. Transdermal estrogen affects thrombotic risk and cardiovascular risk markers less than oral estrogen, which undergoes first pass in the liver.

**Objective:** To evaluate stroke risk with different estrogen administration routes and different doses.

**Design:** Population-based nested case-control study.

**Participants:** All women aged 50 to 79 years in 400 general practices in the United Kingdom, which provided information to a national database.

**Methods:** For each of 15,710 strokes in this group between 1987 and 2006, up to 4 controls were selected from the database. The use of hormone therapy was examined, along with information on route and dose.

**Results:** Of the stroke cases, only 8% (n=1214) had been currently using hormone therapy; of those, 51% took oral estrogen, 6% used low-dose transdermal estrogen, and 2% used higher-dose transdermal estrogen. (The other 41% took progestin or tibolone). The adjusted rate ratio of stroke was no different with transdermal estrogen at doses up to 50 µg/day (0.81; 95% CI, 0.62 to 1.05), compared with the non-use of estrogen. The rate ratio was 28% higher for oral estrogen at all doses (1.28; 95% CI, 1.15 to 1.42). The rate ratio for the use of transdermal estrogen at doses >50 µg/day was 89% higher than for the non-use of estrogen, with a very wide confidence interval (1.89; CI, 1.15 to 3.11) because of few users at these doses. The duration of use was only significantly associated with stroke risk for >1 year of use of oral estrogen; shorter duration of use and short or long duration for transdermal estrogen showed no significant effect on risk.

**Conclusions:** The use of low-dose transdermal estradiol is not associated with an increased risk of stroke above non-use of estrogen, although the researchers warn that "residual confounding...cannot be entirely excluded."

**Reviewer's Comments:** The finding of increased stroke risk with oral estrogen is consistent with other studies, including the Women's Health Initiative (WHI). Since the WHI, research in menopausal hormone therapy has focused on the (biologically plausible) hope that lower dosing, transdermal route, and/or earlier initiation (closer to the menopause transition than in the WHI) might be more beneficial and less risky. Evidence is becoming available to support these factors (ie, the 2010 position statement by the North American Menopause Society). Still, estrogen is being prescribed cautiously now after menopause, with the ideal duration still not clear. The authors of this study rightfully warn that their results do not provide definitive evidence for cerebrovascular safety. (Reviewer-Eliza L. Sutton, MD).

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Keywords: Hormone Replacement Therapy, Menopause, Stroke

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## Sexual Interest, Function Improve on CPAP in Men With OSA

*Outcome of CPAP Treatment on Intimate and Sexual Relationships in Men With Obstructive Sleep Apnea.*

Reishtein JL, Maislin G, et al:

J Clin Sleep Med 2010; 6 (June 15): 221-226

The potential for improvement in sexual interest and functioning may be an important consideration for men with moderate to severe obstructive sleep apnea who are considering CPAP therapy.

**Background:** Obstructive sleep apnea (OSA) impairs sexual interest and functioning.

**Objective:** To evaluate the effect of continuous positive airway pressure (CPAP) therapy on self-reported sexual interest and functioning in men with OSA.

**Participants/Methods:** Men aged 21 to 60 years diagnosed with OSA who were candidates for CPAP therapy and who agreed to participate in the study (n=123) underwent sleep testing and completed questionnaires measuring sleepiness, intimacy, and sexual functioning before starting CPAP and again 3 months later. (Women comprised only 10% of the study group, and factors affecting sexual interest and function are more complicated; the women's results are not reported.)

**Results:** Results were grouped by initial severity of OSA (apnea-hypopnea index [AHI], 20 to <40, 40 to <60, and >60 events per hour). At baseline, participants overall scored lower than normal on the Intimacy and Sexual Relationships (ISR) subscale of the Functional Outcomes of Sleep Questionnaire and scored high for subjective sleepiness on the Epworth Sleepiness Scale. Subjective sleepiness correlated with a low ISR score. After CPAP use for 3 months, ISR scores improved for the entire group, most significantly in those with the most severe OSA. The improvement correlated with improvement in both subjective and objective sleepiness. At baseline, difficulty was reported by 29% for orgasm (declining to 18% on CPAP), 46% for arousal (2% on CPAP), 63% for intimacy (34% on CPAP), and 69% for desire (40% on CPAP); each of these changes was statistically significant, the latter 3 significantly so.

**Conclusions:** In men with moderate to severe OSA, CPAP therapy improves self-reported intimacy, sexual interest, and sexual function.

**Reviewer's Comments:** This is the largest study to date examining the effects of CPAP therapy on sexual dysfunction in men with OSA. It would be interesting to know whether these participants (or their partners) felt that CPAP itself presented any new barriers to intimacy and sexual functioning, because some patients (or their partners) raise this as a concern and, sometimes, as a reason not to use the therapy. In addition, further study of the effects, if any, of CPAP therapy on sexual interest and functioning in women with OSA would be a useful addition to the literature. (Reviewer-Eliza L. Sutton, MD).

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Keywords: Obstructive Sleep Apnea, Sexual Function, Sexuality

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## P-SAP Predicts OSA With Ease, Accuracy

*Derivation and Validation of a Simple Perioperative Sleep Apnea Prediction Score.*

Ramachandran SK, Kheterpal S, et al:

Anesth Analg 2010; 110 (April 1): 1007-1015

Use of the perioperative sleep apnea prediction scoring system preoperatively may improve the diagnosis of OSA.

**Background:** Obstructive sleep apnea (OSA) is common, with a prevalence of approximately 10% or higher in the general population. Its presence increases the risk of myocardial infarction, arrhythmia, stroke and sudden death. Perioperatively, it increases the risk of respiratory failure and prolonged hospital stay. Prior prediction models for OSA are reasonably accurate but are fairly complex, and many have not yet been validated prospectively.

**Objective:** To develop a simple, easy to use, and accurate perioperative sleep apnea prediction (P-SAP) model based on independent clinical predictors in a general surgical population, and to validate this model against standard overnight polysomnography (OPS).

**Design/Methods:** Retrospective, observational study in a large academic medical center that identified patients with OSA and assessed independent predictors derived by logistic regression analysis. From this, a P-SAP scoring system was derived and was then prospectively validated among patients undergoing OPS.

**Results:** Of 43,576 adult patients undergoing anesthesia, 3884 (7.17%) had a documented prior diagnosis of OSA. Independent predictors of OSA were age >43 years, male gender, obesity, history of snoring, diabetes mellitus type 2, hypertension, thick neck, modified Mallampati class 3 to 4, and reduced thyromental distance. P-SAP score  $\geq 2$  had high sensitivity (0.94) but poor specificity (0.32), while a score of  $\geq 6$  had poor sensitivity (0.24) with high specificity (0.91). Validation of this scoring system was performed in 512 patients (with OPS) with similar accuracy.

**Conclusions:** The P-SAP scoring system has dependable accuracy in the diagnosis of OSA perioperatively in a typical university surgical population.

**Reviewer's Comments:** The diagnosis of OSA is important, especially perioperatively, but prior predictive models may be a bit complex and cumbersome in a short preoperative visit. This scoring system is fairly quick and easy to use and has good diagnostic accuracy. Using P-SAP  $\geq 4$  ensures a decent balance of sensitivity (0.67) and specificity (0.77), which is similar to other available screening prediction models. I would prefer a higher sensitivity, but at lower P-SAP scores, the specificity is poor, which would result in significant overdiagnosis. The gold standard for diagnosis is still OPS, but it is not always possible to perform before surgery. From a perioperative care perspective, it would be especially helpful to know if there is a subgroup of patients with specific OSA predictors who are at particularly high risk for postoperative complications. Further study is needed, but this tool should be useful for streamlining and improving accuracy of screening for OSA in the perioperative setting when OPS is not feasible. (Reviewer-Molly Blackley Jackson, MD).

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Keywords: Obstructive Sleep Apnea, Scoring System

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## POLST Form Reveals Preferences on End-Of-Life Care

*A Comparison of Methods to Communicate Treatment Preferences in Nursing Facilities: Traditional Practices Versus the Physician Orders for Life-Sustaining Treatment Program.*

Hickman SE, Nelson CA, et al:

J Am Geriatr Soc 2010; 58 (July): 1241-1248

Use of the Physician Orders for Life-Sustaining Treatment form, available in some states, results in more detailed orders about patients' preferences for end-of-life treatment.

**Background:** The Physician Orders for Life-Sustaining Treatment (POLST) program was designed to improve communication about treatment preferences at the end of life and is available in several states. It consists of a standardized order form that is to be completed by a provider with the patient and includes orders about code status, other life-sustaining treatments, hospital transfer, use of antibiotics, and artificial nutrition.

**Objective:** To assess whether nursing home residents with and without POLST forms differed in the following areas: frequency of orders for end-of-life treatment preferences, management of pain and dyspnea, and the use of potentially life-sustaining treatments including hospital transfer.

**Design:** Retrospective observational cohort study in Oregon, Wisconsin, and West Virginia. The study involved living and deceased skilled nursing facility (SNF) residents aged  $\geq 65$  years.

**Methods:** Every licensed SNF in the 3 states was contacted. Twenty charts were randomly selected at each facility, and data were abstracted.

**Results:** 87% of facilities participated. Charts of 1711 SNF residents were reviewed. The average age of residents studied was 84 years, and the majority of subjects were white women. Residents with POLST forms were more likely to be in hospice and to have died. By definition, all residents with POLST forms had orders about life-sustaining treatment; 87% of non-POLST users had orders about life-sustaining treatments, but only 16% of non-POLST users had orders about life-sustaining treatments other than CPR ( $P < 0.001$  for both comparisons). POLST users with orders for "comfort measures only" were significantly less likely to receive life-sustaining treatments including hospital transfer, intravenous fluids, dialysis, or intubation than residents with POLST full treatment orders, traditional do-not-resuscitate orders, or traditional full code orders. Researchers did not find any differences between POLST users and non-users with respect to assessment and management of pain and dyspnea. Orders in the POLST form regarding antibiotics did not correlate with the use of antibiotics.

**Conclusions:** Residents with POLST forms were more likely to have orders reflecting treatment preferences, but there was no association between POLST form use and antibiotic use or symptom management.

**Reviewer's Comments:** The POLST form seems to be more effective than traditional orders for communicating patient preferences about transfer to the hospital from a nursing home and about potentially life-sustaining treatments. Orders on the POLST form regarding the future use of antibiotics do not seem to affect whether the patient receives antibiotics; I am not surprised by this finding because individual clinicians, patients, and families would have varying opinions about whether antibiotics would enhance comfort or be a burden in a particular case. I use the POLST form frequently and find it to be a useful tool that I hope will eventually be adopted in all states. More information about the POLST program is available at POLST.org. (Reviewer-Susan E. Merel, MD).

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Keywords: End of Life, Advance Directives, Skilled Nursing Facilities

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## Vitamin D May Reduce Fall Risk in Older Patients

*Vitamin D Treatment for the Prevention of Falls in Older Adults: Systematic Review and Meta-Analysis.*

Kalyani RR, Stein B, et al:

J Am Geriatr Soc 2010; 58 (July): 1299-1310

Checking vitamin D levels in elderly patients and starting supplementation in those with a 25-hydroxy vitamin D level <30 may decrease the risk of falls.

**Background:** There is a growing body of evidence suggesting that elderly patients with vitamin D deficiency may be at higher risk of falls, and that vitamin D replacement can help prevent falls.

**Objectives:** To systematically review and analyze randomized controlled trials (RCTs) that have studied the effectiveness of treatment of vitamin D deficiency in adults  $\geq 60$  of age in preventing falls and whether higher doses of vitamin D are associated with greater benefit.

**Design:** Systematic review and meta-analysis.

**Participants/Methods:** A standardized protocol was developed, and the search was done in February 2009. Studies included RCTs (participants  $\geq 60$  years of age) that compared vitamin D treatment with placebo, calcium, or no treatment and that had an explicit definition of a fall and a description of how falls were ascertained. A total of 136 studies underwent full text review and 10 RCTs met inclusion criteria for primary analysis. There were 2932 participants (mean age range, 71 to 92 years) in the studies that met inclusion criteria, and the majority of the participants were women.

**Results:** Methodological quality of the included studies was good. Five studies included community-dwelling adults, 4 included institutionalized patients, and 1 included only hospitalized patients. Four studies included mostly participants with a history of falls or fractures, and 4 included mostly participants who had not fallen. Baseline vitamin D levels were not reported in all studies, and improvement in level was reported in only a few of the studies. Vitamin D supplementation was given as cholecalciferol, ergocalciferol, or alfacalcidol. The duration of treatment was between 1 and 36 months, and native vitamin D dosage ranged from 200 to 1000 IU. In the primary analysis, vitamin D treatment reduced falls with a pooled relative risk of 0.86; this was statistically significant, with a number needed to treat of 15. There was no significant linear association between vitamin D dose or treatment duration and relative risk of falls.

**Conclusions:** Vitamin D supplementation has a modest effect in reducing falls in vitamin D-deficient older adults.

**Reviewer's Comments:** This study reinforces what a few previous meta-analyses have told us, which is that vitamin D supplementation may decrease the risk of falls. The optimum dose and level for fall prevention are still unclear. We do not know whether participants in most of the studies were adequately treated because post-treatment levels were not measured. These studies generally did not make a distinction between injurious and noninjurious falls, which is of concern because other studies of fall prevention have found it difficult to prevent injurious falls. I will continue to check vitamin D levels in elderly patients who fall, and start replacement if they are deficient, while waiting for more good evidence on this topic. (Reviewer-Susan E. Merel, MD).

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Keywords: Elderly, Falls, Prevention, Vitamin D

Print Tag: Refer to original journal article

## Is Dementia Associated With Depression?

*Depressive Symptoms and Risk of Dementia: The Framingham Heart Study.*

Saczynski JS, Beiser A, et al:

Neurology 2010; 75 (July 6): 35-41

A history of depression is associated with an increased risk of dementia in older patients.

**Background:** A meta-analysis of case control trials showed a history of depression doubled the risk of dementia. However, longitudinal studies have been mixed.

**Objective:** To assess the association of depression and incident dementia.

**Design:** Longitudinal, population, cohort study.

**Participants/Methods:** 949 dementia-free subjects of the Framingham cohort were identified and followed for up to 17 years. Incident depression was assessed with the Centers for Epidemiological Studies Depression Scale (CES-D) scaled from 0 to 60, with higher scores indicating more severe depression. Active use of an antidepressant was used as an alternative definition of depression. Biennial Mini-Mental State Examinations (MMSE) and clinical data were used to identify likely cases of dementia. Such subjects subsequently underwent full neurological examination and neuropsychiatric testing. A panel, including a neurologist and neuropsychologist, reviewed all cases of incident dementia and further classified Alzheimer disease (AD) dementia by accepted criteria. Demographics, substance use, concomitant medical conditions, obesity, and particular alleles apolipoprotein E genotype (*APOE*  $\epsilon$ 4) were assessed.

**Results:** The mean age of the 949 participants was 79 years and women comprised 63% of the group. A total of 125 subjects were diagnosed with depression at baseline with CES-D scores  $\geq 16$ , and an additional 39 were identified as depressed based on depression medication prescriptions; 164 subjects developed dementia. Depressed patients were more than 1.5 times more likely to develop dementia in all analysis scenarios, adjusting for demographics, *APOE*  $\epsilon$ 4 genotype, and homocysteine levels (HR, 1.72; 95% CI, 1.04 to 2.84), defining depression including antidepressant prescriptions (HR, 1.67; 95% CI, 1.05 to 2.66). For every 10-point increase in CES-D scores, the risk for developing dementia increased almost 1.5 times (HR, 1.46; 95% CI, 1.18 to 1.79). The risk for AD was also increased (HR, 1.76; 95% CI, 1.03 to 3.01) and had a similar depression severity association (HR, 1.39; 95% CI, 1.11 to 1.75) for every 10-point increase in CES-D score. Adjustment for gender and major vascular risk factors showed a doubling of risk for all dementia and AD (HR, 2.01; 95% CI, 1.20 to 3.31 and HR, 1.97; 95% CI, 1.15 to 3.39, respectively).

**Conclusions:** Depression is associated with an increased risk of dementia in older people.

**Reviewer's Comments:** The strength of this study is the up to 17-year duration of follow-up and the meticulous methodology typical of Framingham studies. It remains unclear whether depression is causative in the development of dementia or an early manifestation of an unfolding dementing process. The authors attempted to address this by reanalyzing the data omitting patients with mild cognitive impairment, and the association persisted. Depression is an episodic condition, yet was only assessed at the start of this study. It would be interesting to see the subsequent incidence of depression at follow-up among subjects with and without dementia. It might speak to the possibility of reverse causality. Nonetheless, I will be far more vigilant in performing screening MMSE on elderly patients with a history of depression. (Reviewer-Genevieve L. Pagalilauan, MD).

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Keywords: Depressive Symptoms, Risk Factors, Dementia

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## SSRIs May Increase Ischemic Stroke Risk in Elderly

*Risk of Ischemic Stroke Associated With Antidepressant Drug Use in Elderly Persons.*

Trifirò G, Dieleman J, et al:

J Clin Psychopharmacol 2010; 30 (June): 252-258

Higher affinity selective serotonin reuptake inhibitors and shorter duration of use increase the risk of ischemic stroke in elderly populations.

**Background:** Pharmacologically, selective serotonin reuptake inhibitors (SSRIs) could be protective for ischemic stroke due to their antiplatelet effect, but they could also be deleterious due to vasoconstriction from increased serotonin effect.

**Objective:** To assess the net effect of antidepressant medication on ischemic stroke risk in elderly patients.

**Design:** Population-based, nested, case-control study.

**Methods:** An analysis was performed of a primary care database in the Netherlands that included 800,000 patients. End points of interest were transient ischemic attack (TIA), stroke, death, and emigration of the practice area. Patients were excluded if they had a stroke, TIA, or cerebral tumor prior to enrollment. Cases were defined as patients  $\geq 65$  years of age with a first time ischemic stroke as defined by CT, specialist diagnosis, or discharge diagnosis. All antecedent antidepressant use was assessed including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and others (including selective norepinephrine reuptake inhibitors [SNRIs] and novel mechanism medications), with attention to the degree of affinity to the serotonin receptor. Controls were matched based on demographics, and covariates included medical illnesses, concomitant medication use, and the indication for antidepressant use.

**Results:** 69,216 people  $\geq 65$  years of age were in the final analysis group; 996 first time ischemic strokes were identified. Current use of SSRIs showed an increased risk of ischemic stroke, (OR, 1.55; 95% CI, 1.07 to 2.25) compared to no effect found for TCAs or other antidepressants (OR, 1.18; 95% CI, 0.73 to 1.91 and OR, 1.01; 95% CI, 0.45 to 2.25, respectively). No dose effect was found for any type of antidepressant, but a shorter duration use of an SSRI had an increased association with ischemic stroke ( $\leq 180$  days: OR, 2.07; 95% CI, 1.24 to 3.46 and  $> 180$  days: OR, 1.14; 95% CI, 0.65 to 1.97). Increased affinity for the serotonin receptor was associated with ischemic stroke, with the largest effect seen for sertraline and paroxetine.

**Conclusions:** In people  $\geq 65$  years of age with depression, current use of SSRIs, especially in the first 6 months, is associated with increased risk of ischemic stroke.

**Reviewer's Comments:** Depression increases risk for morbidity and mortality from other medical conditions, such as cardiovascular disease and diabetes. To further complicate matters, stroke predisposes patients for depression. It makes studies such as this one interesting and harder to apply in a meaningful way for our patients. I may choose medications, such as mirtazapine or citalopram, as first-line treatment due to their tolerability in elderly populations and their low-moderate affinity for the serotonin receptor. There is nothing I can do about the increased risk during the initiation phase. Will I counsel each patient I start on an antidepressant that they are at increased risk for ischemic stroke? Not in most cases. I would if they were high risk for cerebrovascular events, but I would balance it with the understanding that untreated depression carries morbidity and mortality risk as well. (Reviewer-Genevieve L. Pagalilauan, MD).

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Keywords: Elderly Patients, Antidepressant Drugs, Ischemic Stroke

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## CALM Approach to Anxiety Tx Is Superior to Usual Care

*Delivery of Evidence-Based Treatment for Multiple Anxiety Disorders in Primary Care: A Randomized Controlled Trial.*

Roy-Byrne P, Craske MG, et al:

JAMA 2010; 303 (May 19): 1921-1928

A coordinated evidenced-based approach to anxiety treatment improves remission and recovery rates compared to usual care.

**Background:** Although several studies have shown the effectiveness of coordinated evidence-based treatment approaches for depression, similar studies have not been conducted for anxiety disorders.

**Objective:** To compare a flexible treatment delivery model for multiple anxiety disorders to usual care (UC) in the primary care setting (the Coordinated Anxiety Learning and Management [CALM] study).

**Participants/Methods:** Over 1000 primary care patients with anxiety disorders (panic disorder, generalized anxiety disorder, social anxiety disorder, or posttraumatic stress disorder [PTSD]) were referred to an anxiety clinical specialist (ACS) nurse, social worker, or psychologist. The ACS determined if subjects met inclusion criteria; age, 18 to 75 years; *DSM IV* criteria for 1 or more of the anxiety disorders listed above; and scored >7 out of 20 on the Overall Anxiety Severity and Impairment Scale (OASIS), a validated anxiety severity scale. Exclusion criteria were unstable medical conditions, cognitive impairment, suicidality, substance abuse (except alcohol and marijuana), psychosis, or bipolar disease. After computer randomization to intervention or UC, the intervention group received 12 weeks of their preferred treatment, medications, cognitive behavioral therapy (CBT), or both. The ACS administered the CBT to subjects, monitored adherence with a web-based monitoring program, and recommended medication changes via a supervising psychiatrist. The medication protocol recommended selective serotonin reuptake inhibitor or selective norepinephrine reuptake inhibitor antidepressants followed by a combination of antidepressants or an antidepressant and a benzodiazepine.

**Results:** The primary outcome was the result of an anxiety severity tool, the Brief Symptom Inventory (BSI 12). The intervention arm had superior outcomes versus UC at 6, 12, and 18 months for response and remission. Response rates compared to UC were 57% versus 37% at 6 months, 64% versus 45% at 12 months, and 65% versus 51% at 18 months. Remission rates were 43% versus 27%, 51% versus 33%, and 51% versus 37%, respectively. The number needed to treat at 6, 12, and 18 months for response is 4.8, 5.3, and 7.6, respectively, and 6.3, 5.5, and 7, respectively, for remission.

**Conclusions:** A flexible evidence-based anxiety treatment model improved response and remission rates for anxiety, depression, and the quality of anxiety care in primary care settings.

**Reviewer's Comments:** Despite good evidence to substantiate the type and dosage of medications and the components of CBT best for anxiety treatment, there is substantial variation in the approach to therapy in the primary care setting. The CALM study shows that a coordinated, evidence-based approach to anxiety has superior outcomes to our usual practices. Because this was a blended approach including (inclusion of patient preference, a web-based monitoring program, medication and CBT), we cannot tease out the most effective component. CALM offers an innovative model that fosters improved management of anxiety in the outpatient setting. I await further assessment of cost and feasibility analysis for this program. As internists, lessons we can learn are to use objective anxiety assessment tools, optimize the dose and choice of SSRIs or SNRIs, and offer concurrent CBT. (Reviewer-Genevieve L. Pagalilauan, MD).

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Keywords: Multiple Anxiety Disorders, Primary Care, Treatment Options

Print Tag: Refer to original journal article

## Pesticide Exposure Linked to ADHD

*Attention-Deficit/Hyperactivity Disorder and Urinary Metabolites of Organophosphate Pesticides.*

Bouchard MF, Bellinger DC, et al:

Pediatrics 2010; 125 (June): e1270-e1277

Exposure to pesticides (which occurs mostly from intake of nonorganic fruits and vegetables) is associated with attention-deficit/hyperactivity disorder in children.

**Background:** Detectable concentrations of pesticides are not uncommon on nonorganically grown fruits and vegetables. Prior study has linked higher levels of organophosphate pesticide exposure to lower cognitive function and behavioral problems in children. However, no study has assessed the degree of potential harm of the levels of exposure that are typical in the general population.

**Objective:** To understand the association between urinary metabolites of organophosphates and attention-deficit/hyperactivity disorder (ADHD) in youths aged 8 to 15 years.

**Methods:** The National Health and Nutrition Examination Survey was conducted from 2000 to 2004 by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC). The survey represented 1139 children and was carefully administered in order to be representative of the general U.S. population. Interviews with parents were used to assess ADHD diagnostic status by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Urinary dialkyl phosphate (DAP) metabolite levels were measured for a random sub-sample of the survey participants. Exclusion criteria were children who received care in a NICU premature nursery and those with birth weights of <2500 g, given the significance of these as risk factors for developmental disorders.

**Results:** 119 of the 1139 children (10%) met diagnostic criteria for ADHD. Those with higher urinary metabolites of DAPs (especially dimethyl alkylphosphate [DMAP]) were more likely to meet ADHD criteria. A 10-fold increase in DMAP concentration was associated with an odds ratio (OR) of 1.55 (95% CI, 1.14 to 2.10) for ADHD after adjustment for gender, age, race/ethnicity, poverty/income ratio, and urinary creatinine concentration. Dimethyl thiophosphate was the most commonly identified urinary organophosphate metabolite; youth with higher than the median of detectable concentrations had twice the odds of ADHD (OR, 1.93; 95% CI, 1.23 to 3.02) compared with children with undetectable levels.

**Conclusions:** Organophosphate pesticide exposure, even at levels common among U.S. children, is associated with ADHD.

**Reviewer's Comments:** Though this is not a huge study, the findings are frightening. The major source of pesticide exposure for children and adults is dietary consumption of nonorganic fruits and vegetables. United States Department of Agriculture testing in 2008 found that 70% of fruit and vegetable samples were positive for one or more pesticides. Further, the CDC has detected pesticides in blood and urine samples from over 95% of >5,000 Americans tested in their most recent national biomonitoring program. Yikes! Admittedly, there is not much information about how these pesticides affect adults, but this article finds a significant association between higher levels of pesticide exposure and ADHD in children; it also adds to the growing body of literature raising concerns about U.S. agriculture practices and the potential deleterious impact on the health of our nation. (Reviewer-Molly Blackley Jackson, MD).

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Keywords: ADHD, Organophosphate Pesticides, Urinary Metabolites

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## Postpartum Depression -- Not Just for Mom

*Prenatal and Postpartum Depression in Fathers and Its Association With Maternal Depression: A Meta-Analysis.*

Paulson JF, Bazemore SD:

JAMA 2010; 303 (May 19): 1961-1969

Prenatal and postpartum depression is also common among new fathers.

**Background:** Maternal prenatal and postpartum depression has been well studied and is known to be associated with negative outcomes for children and families. However, little is known about paternal depression during the same period and its potential association with maternal depression.

**Objective:** To better understand the rates of paternal prenatal and postpartum depression and its association with maternal depression.

**Design:** Meta-analysis of studies that document rates of paternal depression during partner pregnancy through the first postpartum year. Studies in MEDLINE, PsycINFO, EMBASE, Google Scholar, among others, between 1980 and 2009 were included.

**Methods:** 2 independent raters extracted rates of paternal and maternal depression and correlations from the included studies. Effect sizes were generated and reported as proportions. Study quality ratings were used in the sensitivity analysis.

**Results:** 43 studies (including 28,004 participants) were included after exclusion of duplicates. There was marked heterogeneity in the observed rates of paternal depression, with meta-estimate of 10.4% (95% CI, 8.5% to 12.7%). Studies conducted in the U.S. reported higher rates than international studies (14.1% vs 8.2%). The rate of paternal depression was highest during the 3- to 6-month postpartum period (25.6%). There was a moderate positive correlation between maternal and paternal depression ( $r=0.308$ ).

**Conclusions:** Prenatal and postpartum depression is common among men (10.4%), especially during the 3- to 6-month postpartum period (25.6%). Maternal and paternal depression is correlated.

**Reviewer's Comments:** Maternal prenatal and postpartum depression is present in 41.6% of women between 3 and 6 months postpartum. However, I think few physicians recognize the reality of perinatal depression among new fathers, affecting over 25% of men at 3 to 6 months postpartum. This study is limited by the heterogeneity of methods used in included studies, but still points out a serious public health concern. This study should urge the development of screening tools and early referral for depression among new parents, both male and female. (Reviewer-Molly Blackley Jackson, MD).

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Keywords: Prenatal Depression, Postpartum Depression, Mothers, Fathers

Print Tag: Refer to original journal article

## Fish Oil Not Yet Advisable as Chemoprevention for Breast Ca

*Specialty Supplements and Breast Cancer Risk in the VITamins and Lifestyle (VITAL) Cohort.*

Brasky TM, Lampe JW, et al:

Cancer Epidemiol Biomarkers Prev 2010; 19 (July): 1696-1708

For unknown reasons, women with coronary heart disease in the VITamins And Lifestyle study had a higher risk of breast cancer diagnosis with use of a fish oil supplement.

**Background:** Many people take supplements in hopes of improving health, including potentially reducing their risk of cancer, but there are few studies demonstrating beneficial health outcomes for supplements.

**Objective:** To evaluate non-vitamin, non-mineral supplements for potential effect on breast cancer risk.

**Design/Participants:** Prospective observational study of 35,016 postmenopausal women from 50 to 74 years of age with no prior breast cancer.

**Methods:** Participants completed a baseline questionnaire in 2000 to 2002 questions regarding known breast cancer risk factors and supplement use (current and over the prior decade). Subsequent new diagnoses of invasive breast cancer were identified through the Surveillance, Epidemiology, and End Results (SEER) registry. The average follow-up was 6 years.

**Results:** Current use of fish oil was associated with reduced risk of breast cancer (hazard ratio [HR], 0.68; 95% CI, 0.50 to 0.92). More specifically, current use of fish oil was associated with reduced risk of early-stage breast cancer (HR, 0.57; 95% CI, 0.38 to 0.84) and ductal breast cancer (HR, 0.56; 95% CI, 0.38 to 0.83).

However, the risks of lobular cancer and of later-stage breast cancer were not affected by fish oil use.

Hormone receptor status in cancers was unrelated to fish oil use. Interestingly, among women with coronary heart disease, fish oil was associated with a doubling of breast cancer risk. Neither former use of fish oil nor any other non-vitamin, non-mineral supplement (including grape seed, soy, and melatonin) showed any association with change in breast cancer risk.

**Conclusions:** Fish oil should be studied further as a potential chemopreventive measure for breast cancer, but should not yet be advised for use for this purpose.

**Reviewer's Comments:** While headlines like "fish oil may reduce breast cancer" may encourage women to take (and physicians to advise) supplements for this purpose, the true test for any cancer prevention measure is reduction in all-cause mortality. Reduction in risk of early stage disease of 1 pathologic type is interesting, but the intervention in question should be examined in a randomized prospective manner, for a longer duration, and with attention to all significant health outcomes to ascertain efficacy. Current fish oil use could be associated with reduced likelihood of early-stage breast cancer diagnosis by a mechanism unrelated to disease prevention, such as a reduced likelihood of obtaining mammograms (for some reason) or reduced sensitivity of mammography for early ductal disease. Finally, the finding of increased cancer risk from supplementation in 1 group (women with heart disease) suggests potential confounding factors may be in play. (Reviewer-Eliza L. Sutton, MD).

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Keywords: Breast Cancer, Prevention, Fish Oil

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