In diabetics taking insulin therapy, the addition of metformin results in a decline in vitamin B$_{12}$ levels over time compared to placebo, and a significant percentage of patients develop vitamin B$_{12}$ deficiency.

**Background:** Metformin is frequently used in the treatment of type 2 diabetes. Metformin has been shown to decrease vitamin B$_{12}$ absorption. Vitamin B$_{12}$ is important in the metabolism of homocysteine, and deficiency can result in elevated homocysteine levels. In turn, elevation of homocysteine is an independent risk factor for cardiovascular disease.

**Objective:** To determine the effects of long-term metformin therapy on vitamin B$_{12}$, folate, and homocysteine levels.

**Design:** Randomized placebo-controlled trial.

**Participants/Methods:** Patients were recruited from community outpatient clinics in the Netherlands as part of the HOME (Hyperinsulinemia: The Outcome of its Metabolic Effects) trial. All patients were treated with insulin for 12 weeks while other diabetes medications were discontinued. They were then randomized to add metformin 850 mg or placebo 3 times a day and followed for an additional 52 months. The primary end points were vitamin B$_{12}$, folate, and homocysteine levels, which were drawn at 0, 4, 17, 30, and 52 months.

**Results:** 390 patients were randomized, and 72% completed the trial on their assigned medication. Compared to patients taking placebo, metformin therapy was associated with a 19% decline (95% CI, −24% to −14%; $P <0.001$) in vitamin B$_{12}$ levels, a nonsignificant slight decrease in folate levels, and an increase in homocysteine levels. Low vitamin B$_{12}$ levels were evenly distributed at baseline, but at the end of the trial, 9.9% of the metformin group compared to 2.7% of the placebo group had frank B$_{12}$ deficiency (<150 pmol/L), and 18.2% taking metformin versus 7.0% on placebo had low vitamin B$_{12}$ levels (150 to 220 pmol/L). Considering a low B$_{12}$ level as the outcome, the number needed to harm was 8.9 over 4.3 years of treatment. In patients taking metformin, vitamin B$_{12}$ levels declined over time.

**Conclusions:** In diabetics taking insulin therapy, the addition of metformin results in a decline in vitamin B$_{12}$ levels over time compared to placebo, and a significant percentage of patients develop vitamin B$_{12}$ deficiency.

**Reviewer's Comments:** This relatively long-term study reinforces the risk of developing vitamin B$_{12}$ deficiency in patients with type 2 diabetes who are taking metformin. It makes sense to monitor B$_{12}$ levels in our diabetics on metformin and replete as needed. Whether this drug-induced B$_{12}$ deficiency results in adverse clinical outcomes is not addressed here, but a study addressing that specific issue is unlikely. (Reviewer-Deborah L. Greenberg, MD).

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Keywords: Metformin, Diabetes, Side Effects

Print Tag: Refer to original journal article
Clinically significant depression appears to increase the risk of the onset of diabetes.

Background: Both diabetes and major depressive disorder have captured attention as chronic diseases emerging to be primary health challenges of the next century. Several longitudinal studies suggest that depression is a risk factor for development of diabetes; however, those studies, as these authors point out, may have used inadequate measures of depression, such as self-reporting. Therefore, what was counted as "depression" may not have been diagnostically robust.

Objective: To better characterize the history and severity of depression of subjects in a population sample.

Methods: This study was part of a larger effort in Zaragoza, Spain, that longitudinally followed an adult population and documented the incidence and risk factors of depression and dementia. A potential sample was randomly selected and recruited from the general population. Subjects needed to be aged ≥55 years and without dementia at baseline. Only subjects from the study who were also without diabetes at baseline were included in the analysis. Participating subjects had baseline and then 2 waves of repeat interviews that included assessments of cognition and dementia, functional activity, personal and family medical history, and various co-occurring health factors (ie, alcohol and tobacco use, body mass index, hypertension, etc). Depression was evaluated using a structured diagnostic interview that identified the level of severity of symptoms, characterized depression as first or recurring, and identified any pattern of use of antidepressants.

Results: Of the total sample of 3521 subjects, 379 (10.8%) were diagnosed with depression. In follow-up waves, the overall incidence of new cases of diabetes was significantly higher among depressed subjects (19.70 per 1000 person-years) compared to nondepressed subjects (12.36 per 1000 person-years). This association between having depression and the incidence of diabetes held when controlling for sociodemographic variables, diabetes risk factors, and antidepressant use. The diabetes incidence was, interestingly, greatest among those with nonsevere and persistent depression and a history of depression. The overall impact on the risk of having clinically defined depression was to increase the likelihood of diabetes onset by 65%.

Conclusions: Having depression appears to confer an increased risk of diabetes.

Reviewer's Comments: The study specifically offered itself as a corrective trial to previous studies of the relationship between diabetes and depression by clarifying how depression is measured. However, it is precisely on this point that the study needed to provide more detail. Using a scale not commonly used in this literature and a limited description in the results made the gradations of "severe," "nonsevere," and "clinically significant" hard to judge. That being said, the paper will extend attention to this potentially important connection. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Major Depression, Diabetes

Print Tag: Refer to original journal article
Dietary added sugars are correlated with adverse lipid profiles, independent of other dietary components, biometrics, or health indicators.

**Background:** Dietary fat can cause adverse effects on lipid profiles, and carbohydrates have also been shown to cause similar changes. We are seeing more excessive dietary added sugars in our food, so what, if any, direct effect do they have on lipids?

**Objective:** To determine what effect added, or discretionary, dietary sugar has on lipid profiles, particularly when controlled for biometrics, health conditions, and other dietary factors.

**Design/Methods:** Cross-sectional analysis performed on the NHANES population survey on diet and health indicators, including adults aged ≥18 years. Participants were assessed for epidemiologic and biometric measures, and all provided fasting blood samples. Patients were excluded if they were pregnant, had diabetes, had extremes of body mass index (BMI) or triglyceride levels, or if they were taking cholesterol-lowering medications. "Added sugars" were defined as sweeteners that provide energy but few micronutrients or phytochemicals. Examples include high-fructose corn syrup.

**Results:** 6113 study participants were grouped into 5 main categories by proportion of dietary intake derived from added sugars: those who had <5%; 5% to 10%; 10% to 15%; 15% to 20%, and >25%. Overall findings were that statistically significant decreases in HDL levels, and increases in triglycerides and LDL levels, were found for patients taking larger amounts of added sugars. In other words, the more added sugar in the diet, the more adverse the lipid profiles, especially among women. No significant trends were noted between consumption of added sugars and either the BMI or waist circumference. However, the lowest sugar consumption group was found to have had a mean loss of 0.3 pounds of body weight compared to an average gain of 2.8 pounds in the highest consumer group.

**Conclusions:** Dietary added sugars appear to be statistically correlated with adverse lipid profiles.

**Reviewer's Comments:** We know that diabetes, and prediabetic conditions such as impaired fasting glucose and impaired glucose tolerance, are independent risk factors for cardiovascular disease. This study suggests a more complex direct interaction between sugar intake, separate from carbohydrate intake, and lipid metabolism. The authors postulate that added sugars may act through the monosaccharide fructose, stimulating hepatic lipogenesis, triglyceride synthesis, and secretion of very-low-density lipoproteins. What we do not know is whether this adverse impact on lipid profiles actually affects cardiovascular outcomes as well. Since added sugars are a discretionary component of our diet, they advocate specific nutritional guidance that explicitly calls out added sugars as being distinct from fiber and complex carbohydrates. Younger, low-income, non-Hispanic blacks were found to have higher sugar diets. If the implication of this study is that added sugar is widely prevalent and more harmful than previously believed, then health disparities may also be expected to worsen over time. (Reviewer-Emily Y. Wong, MD).

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Keywords: Sugars, Lipid Profile, Cholesterol, Triglycerides

Print Tag: Refer to original journal article
Does Exercise Increase Libido?

Physical Function and PDE5 Inhibitors in the Treatment of Erectile Dysfunction: Results of a Randomized Controlled Study.

Maio G, Saraeb S, Marchiori A:

J Sex Med 2010; March 30 (): epub ahead of print

It is time to tell men taking prescription drugs for erectile dysfunction that exercise can make this pill work much better.

**Background:** Several observational studies had suggested that exercise reduces the risk of erectile dysfunction (ED), but no randomized trial of exercise and phosphodiesterase type 5 (PDE5) inhibitors had ever been completed.

**Objective:** To determine the synergistic relationship between PDE5 inhibitors and exercise.

**Design/Participants:** Randomized, open-label study of 60 patients with ED.

**Methods:** Half the participants took the PDE5 inhibitor, and the other half combined the pill with regular exercise. Men in this trial were overall inactive at baseline and were instructed to choose any form of exercise (along with intensity and duration information) if they were in the exercise group. Men with a history of radical pelvic surgery were excluded.

**Results:** Mean age of participants was 50 years, and body mass index was 27 (overweight). A significant improvement was observed in all aspects of the International Index of Erectile Function-15 except the orgasm domain for men who exercised ≥3 hours a week compared to the group that took only the ED pill. Erectile function, confidence, sexual desire, intercourse satisfaction, and total satisfaction were all statistically significantly improved over the PDE5 group alone. There was no significant difference between testosterone levels between groups, but, within the exercise group, there was an increase only in testosterone. The frequency of intercourse was nonsignificantly greater compared to the pill-only group.

**Conclusions:** A PDE5 inhibitor along with regular exercise is more effective compared to just taking a PDE5 inhibitor alone.

**Reviewer's Comments:** Heart health=penile health (Moyad, circa 1995 to present day). Is this really such a shock? Yes! It is shocking because there was a significant improvement in libido. PDE5 inhibitors were never found to significantly and consistently improve libido. This is the Achilles heel of the PDE5 inhibitors (along with cost and side effect issues). However, if patients can be told that now taking PDE5 inhibitors along with exercise may improve libido, there should be more excitement in taking these drugs. In fact, perhaps ED drugs should also come with a free treadmill with every prescription (one has to be allowed to dream). There was no significant difference in intercourse frequency, which should have been explored or theorized as to "why" in the follow-up. Finally, don't you find it interesting that there was no exercise-only (no-pill) group? Is it possible that exercise alone could have beaten the pill? We are left to ponder this thought, but, in the meantime, it was found that the drug not only worked better with exercise, but it also improved the diversity of benefits that could be offered with these pills. Bring on that new commercial, boys and girls! (Reviewer-Mark A. Moyad, MD, MPH).

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Keywords: Erectile Dysfunction, Treatment, PDE5 Inhibitors

Print Tag: Refer to original journal article
Do Fruits, Vegetables Really Prevent Cancer?

Fruit and Vegetable Intake and Overall Cancer Risk in the European Prospective Investigation Into Cancer and Nutrition (EPIC).

Boffetta P, Couto E, et al:

J Natl Cancer Inst 2010; 102 (April 21): 529-537

Background: Fruit and vegetable consumption receives a good deal of promotion in the area of cancer prevention, but prospective research over the past several years has not provided convincing evidence to support this hype. However, a large and longer follow-up epidemiologic study was needed to provide greater clarity on this issue.

Objective: To determine the impact of fruit and vegetable consumption on the risk of a variety of cancers in one of the largest epidemiologic studies ever completed.

Design/Methods: This prospective study involved 142,605 men and 335,873 women who were free of cancer; >30,000 cancer cases were identified during this time period. Median follow-up was almost 9 years.

Results: A significant 4% reduction was observed in the risk of being diagnosed with any cancer for every 2 extra servings per day of fruits or vegetables. Individuals who consumed the highest amount (>6 servings a day) of fruits and vegetables compared to the lowest received a ≤10% reduction in risk. Individuals who consumed more fruits and vegetables also were more physically active, drank less alcohol, were less likely to smoke, and received more education, on average, compared to those consuming less produce.

Conclusions: A small and weak inverse association was found for fruit and vegetable consumption and cancer risk.

Reviewer’s Comments: Just because something sounds healthy and productive does not mean it should get a free pass in terms of research scrutiny. It still drives me nuts (not a fruit or vegetable) when I hear cancer organizations and "experts" promoting fruit and vegetable consumption as the miracle way to reduce cancer risk. I believe this is promoted because of ignorance or simply to promote an agenda. However, if someone trying to reduce their risk of cancer is told to eat ≥5 servings a day (this has been advertised for decades) because it can affect cancer, it is sad that we are not providing more objective candor. I tell patients to eat more fruits and vegetables because it makes them feel fuller (fiber, folks!) and may possibly reduce blood pressure and weight, but vegetables have more data available compared to fruits because there are fewer calories and carbohydrates or because there is less simple sugar in vegetables. Personally, I think someone consuming a lot of fruits may also gain weight (fruits contain calories and simple sugars such as fructose). In reality, we also have to accept the results of numerous recent studies that suggest a minimal or even no impact of eating tons of fruits and vegetables on cancer risk, but it could just be that eating these things is simply a marker of overall healthy human behavior, which is why people thought they were so effective. (Reviewer-Mark A. Moyad, MD, MPH).

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Keywords: Cancer, Nutrition, Fruits, Vegetables

Print Tag: Refer to original journal article
In this large community-based program, the myocardial infarction rate decreased, as did short-term mortality after myocardial infarction.

**Background:** Over the last 10 years, there have been few data on changing rates of myocardial infarction (MI).

**Objective:** To examine trends in the incidence of MI, with specific attention to differences between non–ST-segment elevation MI (NSTEMI) and ST-segment elevation MI (STEMI), as well as severity of infarct and short-term mortality.

**Design:** Retrospective, observational cohort study.

**Methods:** Kaiser Permanente Northern California, an integrated health care delivery system, cares for >3 million people. From 1999 to 2008, hospitalizations for MI were identified for members aged ≥30 years. These events were then labeled as either NSTEMI or STEMI from billing codes (with chart reviews of random charts to ensure accuracy). Laboratory results, including creatinine kinase and troponin levels, were obtained from these hospitalizations. Thirty-day mortality rates were determined and adjusted for sociodemographic characteristics, prior heart disease, cardiovascular risks, and other illnesses. Medication use prior to MI was available for the majority of patients.

**Results:** >46,000 patients with an MI were identified in this review. The overall rate of MI peaked in 2000 and then decreased each year (287 cases per 100,000 person-years down to 208, a 24% reduction). This was primarily due to a significant decrease in the rates for STEMI, from 133 cases/100,000 person-years to 50 cases/100,000 person-years. The overall proportion of STEMI dropped from 47% in 1999 to 23% in 2008. The overall 30-day fatality rate dropped from 10.5% to 7.8%. This was due to a drop in NSTEMI mortality, as STEMI fatality rates did not improve. Revascularization procedure rates did increase over the duration of the study.

**Conclusions:** In the Kaiser Permanente population, the rate of MI and the case-fatality rate both decreased over a 9-year period. This was primarily due to a decrease in the number of STEMIs and improved mortality after NSTEMI.

**Reviewer’s Comments:** There is certainly some encouraging news in this analysis. First of all, it appears that when preventive measures are put in place, there may well be some tangible improvement in outcomes, including fewer heart attacks. It is important to realize that the reported quality measures, such as blood pressure and lipid control, were better than in most settings. Therefore, although these results may not be completely generalizable, benefits of improving preventive measures have been reinforced. (Reviewer-Mark E. Pasanen, MD).
Background: Warfarin is a commonly prescribed medication with clear risks associated with over- or underdosing. The initial period of dose titration is particularly difficult, with increased risk of bleeding or thrombosis during this time. There are genetic polymorphisms that account for the variation in stable outpatient dosing in patients taking warfarin therapy. Simple genetic tests are available to evaluate for these genes, but the clinical utility of these tests has not been established.

Objective/Methods: The study was intended to address typical clinical practice, therefore patients were drawn from patients who had prescription plans managed by Medco, which included patients from varied parts of the country, differing clinical practices, and different insurance plans. Any patient aged 45 to 70 years initiated on warfarin was eligible, provided they were without a preceding warfarin prescription in the last 180 days or a hospitalization >7 days preceding warfarin prescription. Overall, 896 patients were genotyped and constituted the study group, and were matched 3:1 to historical controls from the same plans. Genotype testing results and the interpretation of the results as relates to warfarin dosing were delivered to the patients' physicians, but no recommendations regarding specific dosing were made. The primary end point was hospitalization in the first 6 months following initiation of therapy. The results were delivered with clinical considerations, including relative sensitivity and recommendations such as dose decrease and frequent monitoring or likely to experience normal response to warfarin.

Results: Average age was 65 years, and 61% were men. Patients in the intervention group had 28% fewer hospitalizations than the historical controls (18.5% vs 25.5%) and 27% fewer hospitalizations for bleeding or thrombosis (6.0% vs 8.1%). Similar differences (31% and 40%) were seen in adjusted models. There was no difference in hospitalizations between the historical control groups.

Conclusions: Genotyping resulted in an approximately 30% reduction in hospitalizations in adults starting warfarin therapy, and therefore should be considered for all outpatients starting warfarin.

Reviewer’s Comments: Pharmacogenetics continues to evolve, particularly in finding appropriate use in daily clinical practice. This study would suggest that warfarin dosing could be beneficially influenced by simple testing. This study was representative of the response of standard clinical practice to the interpretation provided by the testing results, arguing that the results can be applied broadly without specific protocols beyond those used in usual practice; whether this is cost-effective remains to be seen. (Reviewer-Karen Stout, MD).

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Keywords: Warfarin Genotyping

Print Tag: Refer to original journal article
This retrospective study of an administrative database found that patients at highest risk of stroke were no more likely to receive warfarin than were patients at the lowest risk.

**Background:** Clinicians must weigh relative risks and benefits of anticoagulation to reduce the risk of stroke in patients with atrial fibrillation (Afib). Some small studies have suggested that anticoagulation tends to be underused because of the overestimation of potential harm of anticoagulation, the underestimation of the potential risk of stroke, or conceivably an unconscious bias against actions that may cause harm. It remains unknown whether real-world practice is in accord with established guidelines.

**Objective:** To examine whether anticoagulation prescribing practices are in accordance with established guidelines in data derived from a large claims database.

**Design/Methods:** Retrospective cohort study of adult patients with Afib or atrial flutter (AF). Subjects were continuously enrolled (≥18 months) in health insurance programs (commercial and Medicare) that are included in a commercially available claims database (US MarketScan). The index diagnosis of AF was defined as the first diagnosis of Afib or flutter after at least 12 months of continuous enrollment, followed by at least 6 subsequent months of clinical data (claims and prescription data for each patient spanned at least 18 months). Warfarin use was obtained from pharmacy claims data. Stroke risk was calculated by the CHADS² score.

**Results:** >170,000 patients from the MarketScan database were included in the study: 51,097 (30.3%) had newly diagnosed AF, and 119,486 (69.7%) had pre-existing AF. Mean duration of continuous health insurance program eligibility was 41 months, and mean age of patients was 73.5 years. The distribution of CHADS² scores in the cohort was as follows: low risk, 20% (CHADS² = 0); moderate risk, 61.6% (CHADS² = 1 to 2); and high risk, 18.4% (CHADS² = 3 to 6). Warfarin was prescribed to 42.6% of the cohort as a whole. Less than half the patients were prescribed warfarin in each of the CHADS² groups, whether low, intermediate, or high risk.

**Results:** Less than half the patients with AF were treated with warfarin. The low utilization of warfarin was seen across a spectrum of patients at low, medium, and high risk for stroke.

**Conclusions:** According to the authors, “these data suggest that guideline recommendations that anticoagulation should be provided in accordance with stroke risk in atrial fibrillation patients are not routinely followed in clinical practice.”

**Reviewer’s Comments:** Reasons for choosing not to use anticoagulation in these patients with AF could not be captured from this database but were certainly influenced by clinicians’ perceptions of potential harms associated with anticoagulation. Nonetheless, it is troubling that prescriptions for anticoagulation in this real-world cohort did not correlate with validated measures of stroke risk. It is unclear how to improve adherence with therapies we know to be beneficial in AF, although more widely accepted tools to assess bleeding risk might be helpful. (Reviewer-Paul R. Sutton, PhD, MD).
Most Patients Do Not Recognize Symptoms of TIA, Minor Stroke

Population-Based Study of Behavior Immediately After Transient Ischemic Attack and Minor Stroke in 1000 Consecutive Patients: Lessons for Public Education.

Chandratheva A, Lasserson DS, et al:

Stroke 2010; 41 (June): 1108-1114

Almost 70% of patients with transient ischemic attack and minor stroke fail to recognize the cause of their symptoms, and 30% delay seeking care for >24 hours. The majority of patients present to their primary care provider.

Background: The opportunity for improved outcome after stroke with thrombolytic therapy fueled interest in reducing delays between symptom onset and treatment. Comparable efforts for transient ischemic attack (TIA) and minor stroke are lacking. Since guidelines now recommend medical evaluation within 24 hours of symptoms, it is critical to understand reasons for delays in seeking care.

Objective: To examine patient behavior immediately after TIA and minor stroke in relation to clinical features, symptom recognition, and perceived stroke risk.

Design: Population-based study.

Participants/Methods: 1000 consecutive patients from the Oxford Vascular Study presenting with TIA or minor stroke were identified from surveillance of hospital admissions, emergency departments and dedicated TIA clinic registrations, review of diagnostic codes, and searches of cranial and carotid imaging. Minor stroke was defined as a National Institutes of Health Stroke Scale score ≤5. Patients were interviewed by study physicians soon after initial presentation. Cases were classified as TIA or stroke using standard definitions.

Results: 459 patients presented after TIA, and 541 after minor stroke. Mean age was 73 years. Of patients, 77% with TIA and 72% with minor stroke saw their primary care physician rather than seeking emergency care. Also, 67% of TIA and 74% of minor stroke patients sought care within 24 hours; 47% of TIA and 46% of minor stroke patients sought care within 3 hours. Sixty-eight percent of TIA patients and 69% of minor stroke patients did not know the cause of their symptoms. TIA patients who failed to correctly recognize their symptoms were less likely to seek emergency services. TIA patients were more likely to delay seeking medical care if they did not have motor or speech impairment ($P<0.001$), if symptoms were brief (<60 minutes; $P<0.001$), and if they were aged <60 years ($P=0.075$). Patients with TIA occurrence on a weekend versus weekday delayed seeking care for 25.1 versus 3.0 hours ($P<0.0002$), respectively. Age, sex, and socioeconomic factors were unrelated to symptom recognition or treatment delays. Individuals with atrial fibrillation and prior stroke were more likely to recognize symptoms and seek care, but those with prior TIA, myocardial infarction, hypertension, and smoking history were not.

Conclusions: 70% of patients with TIA and minor stroke fail to recognize the cause of their symptoms, and 30% delay seeking care for >24 hours.

Reviewer's Comments: The results of this study underscore the opportunity for public education to ensure that people with TIA and minor stroke symptoms receive prompt evaluation and treatment. Primary care physicians are often the point of first contact and should have systems in place to appropriately triage high-risk TIA patients. While it is encouraging that higher-risk patients with motor or speech disturbance or longer duration of symptoms present earlier, efforts to optimize treatment for TIA and minor stroke in order to prevent more devastating strokes are needed. (Reviewer-Elaine F. Sachter, MD).

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Keywords: Transient Ischemic Attack, Stroke, Symptom Recognition

Print Tag: Refer to original journal article
UAE Offers Greater Symptom Improvements, Fewer Complications

Uterine Artery Embolization Versus Abdominal Myomectomy: A Long-Term Clinical Outcome Comparison.

Narayan A, Lee AS, et al:
J Vasc Interv Radiol 2010; 21 (July): 1011-1017

Uterine artery embolization has comparable effectiveness when compared with myomectomy in reducing symptoms related to uterine leiomyomas.

Background: Traditional therapy for uterine leiomyomas has consisted of hysterectomy or abdominal myomectomy. Recent studies suggest that uterine artery embolization (UAE) is associated with comparable improvements in symptoms versus abdominal myomectomy. However, very few studies have compared long-term outcomes between these patient populations.

Objective: To compare long-term outcomes in patients who received UAE versus myomectomy based on self-reported patient symptoms and the number of repeat interventions following the initial procedure.

Design/Participants: Retrospective cohort study of 247 women who received a UAE or abdominal myomectomy between 2000 and 2002 in a single tertiary care hospital.

Methods: The authors were able to contact 185 women; of these, 87 (47.0%) received UAE and 98 (53.0%) received an abdominal myomectomy. Questionnaires were used to evaluate symptom severity before and after the procedure, pregnancy rates, and satisfaction with the procedure. Chart reviews were performed to supplement analyses. The study has a mean follow-up time of >5 years.

Results: After treatment, UAE recipients reported fewer symptoms (score, 15.0) than did those who received myomectomies (score, 22.6). There were significant improvements in heavy bleeding, passing blood clots, fluctuations in the duration of menstrual periods, fluctuation in the length of monthly cycles, and feelings of fatigue. Symptoms of tightness or pressure in the pelvic area, frequent urination during daytime hours, and frequent nighttime urination were not significantly improved. Patients who underwent abdominal myomectomies were more likely to have other gynecological procedures after their initial surgery, although the results were not statistically significant. UAE recipients were less likely to attempt to get pregnant, but those who did had a 66.7% success rate compared with 58.8% for patients who underwent myomectomy. There was no difference between groups when it came to satisfaction with the procedure, reported effectiveness of symptom relief, and recommendation of the procedure to others. Patients who underwent UAE had fewer hospital days and underwent fewer transfusions.

Conclusions: This study demonstrates that UAE recipients are more likely to report greater improvements in symptoms and to have fewer complications. Most important is that improvements in symptoms persisted during long-term follow-up for patients in both treatment groups. Fewer UAE recipients attempted pregnancy. This is in line with guidelines from the Society of Interventional Radiology that suggest UAE is a relative contraindication for women who wish to retain fertility.

Reviewer's Comments: Despite study design weaknesses, the valuable information in the report regarding long-term symptomatic relief with UAE is encouraging. Furthermore, fewer days in the hospital combined with a lower rate of complications serve as supporting factors for UAE. (Reviewer-Waseem A. Bhatti, MD).

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Keywords: Uterine Artery Embolization, Abdominal Myomectomy, Outcomes

Print Tag: Refer to original journal article
Limit chronic use of opioid medications in patients aged ≥60 years with non-cancer pain.

**Background:** As degenerative diseases progress, many older adults develop chronic non-cancer pain. Many pain-relieving medications have increased side effects in the elderly. There is a concern for falls and fractures in older patients taking opioid medications.

**Objective:** To assess the relationship between chronic opioid dose and fractures in older adults.

**Design:** Population-based cohort study.

**Participants/Methods:** Subjects were drawn from the Group Health Cooperative, which provides full care to its patients and maintains centralized clinical and pharmacy databases. Patients were eligible for inclusion if they were aged ≥60 years, had non-cancer pain, and had initiated and continued opioid pain medication for at least 90 days. The average daily dose of opioid medications was calculated in morphine equivalent dose (MED) and separated into quartiles: 0, 1 to 19 mg, 20 to 49 mg, and >50 mg for each 90-day interval. Non-vertebral fractures occurring between 2000 and 2006 were recorded, as were consequences of these fractures.

**Results:** 2341 patients were included in the cohort. The most common pain diagnoses were back pain, extremity pain, and osteoarthritis. Average patient age at initiation of opioids was 73 years, and 65% were women. Average daily MED was 12.8 mg. Patients were followed up for a mean of 32.7 months. There were 320 non-vertebral fractures during this period, with an annual fracture rate of 5%. More than one third of patients were hospitalized within 2 days of their fracture, almost one fourth entered a nursing facility within 1 month, and 2% died within 2 months of their fracture. The annual fracture risk was 28% (P =0.06) higher in all patients currently taking opioids compared to those who were not. The risk was particularly high in those patients taking >50 mg MED at 9.9% annually (HR, 2.00; P =0.005).

**Conclusions:** Chronic opioid medications increase the risk for non-vertebral fractures in older adults living in the community, especially those taking more than the equivalent of 50 mg morphine per day.

**Reviewer's Comments:** This study confirms what many of us fear when using opioid medications in older patients: Fractures and significant consequences of these fractures are increased. For each patient, benefits and potential risks of any medication must be considered. If opioids are initiated, the lowest possible dose should be used, and patients should be re-evaluated periodically to determine if these medications remain appropriate. (Reviewer-Deborah L. Greenberg, MD).
How to Diagnose Hypogonadism in Aging Men

Identification of Late-Onset Hypogonadism in Middle-Aged and Elderly Men.

Wu FC, Tajar A, et al:

N Engl J Med 2010; June 16 (): epub ahead of print

Late-onset hypogonadism should be defined as presence of sexual symptoms along with low testosterone levels.

**Background:** As men age, it is not uncommon to discover low testosterone levels. Aging men also frequently describe problems with energy level, sexual function, and psychological state. Therefore, it has been a bit difficult to determine the relationship between low testosterone levels and various symptomatic complaints. **Objective:** To help better define late-onset hypogonadism by characterizing symptoms associated with low testosterone levels and by finding the testosterone thresholds at which point symptoms become more common. **Design:** Random, observational population study. **Participants:** Men aged 40 to 79 years were randomly invited from population and primary care sites to participate in the European Male Aging Study (EMAS). No specific inclusion or exclusion criteria were used. **Methods:** Men filled out questionnaires on health status, medical background, and sociodemographic status. They also underwent physical, cognitive, and lab testing. The cohort was randomly divided into training and validation groups. Items from questionnaires were screened to identify which questions were associated with low testosterone levels. Next, models were used to determine levels of testosterone below which the likelihood of a symptom was significantly greater than for the overall group. Finally, hypotheses were tested in the validation group. **Results:** 3219 men were included in the analysis (average age, 60 years). Overall, 17% had a testosterone level <11 nmol/L (4% were <8 nmol/L). Nine questions were found to have associations with testosterone level. These included 3 questions on sexual symptoms (morning erections, libido, and erectile function); 3 on physical symptoms (vigorous activity, walking, and bending); and 3 on psychological symptoms (sadness, loss of energy, and fatigue). Sexual symptoms were common, affecting >25% of men enrolled. A threshold testosterone level at which symptoms became more likely was only consistently detected for sexual symptoms (for testosterone level <8 to 11 nmol/L and free testosterone <220 pmol/L). Thresholds for physical and psychological symptoms were not well defined. **Conclusions:** Late-onset hypogonadism should be defined as presence of sexual symptoms along with low testosterone levels. **Reviewer’s Comments:** As the authors point out, differences in mean testosterone levels were minimal between symptomatic and asymptomatic men, reminding us that the association between testosterone levels and symptoms is quite weak. As well, sexual symptoms are quite common, and should be attributed only to androgen deficiency with levels below the thresholds noted above. Free testosterone was primarily additive when total values were borderline. Using the authors’ criteria to include those with low testosterone levels and all 3 sexual symptoms, only approximately 2% of men in this study met the definition for late-onset hypogonadism. This is lower than rates of biochemical deficiency and could decrease unnecessary testosterone replacement. (Reviewer-Mark E. Pasanen, MD).

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Keywords: Testosterone, Hypogonadism, Testosterone Deficiency

Print Tag: Refer to original journal article
Etanercept, infliximab, and adalimumab all have high benefit-to-risk ratios in patients with psoriasis.

**Background:** Tumor necrosis factor (TNF) antagonists are so mainstream now that we are all quite comfortable prescribing them for our psoriasis patients. However, we also acknowledge the potential risk of noninfectious and infectious adverse events from these drugs. How great is that risk? One way to report and understand risk is as a percentile probability. Another way is to calculate risk-benefit ratios as a function of the number needed to treat (NNT) for efficacy versus the number needed to harm (NNH). Another method is through calculation of the number of patient-years of treatment that would be expected to result in a sentinel event.

**Objective:** To determine the benefit versus risk for adalimumab, etanercept, and infliximab in the treatment of psoriasis.

**Design:** Comprehensive literature review with data analysis.

**Methods:** The authors integrated data from published literature and posters presented at national, regional, and international dermatology congresses. For the NNT analysis, they used various efficacy measures such as the Physician’s Global Assessment and the Psoriasis Area and Severity Index (PASI 75) scores. The authors also looked at corresponding data of the percentages of patients reporting adverse events, serious adverse events, and selected adverse events of special interest.

**Results:** The authors found that the NNT for PASI 75 was 1.6 for adalimumab 40 mg every other week, 3.2 for etanercept 50 mg weekly or 25 mg twice weekly, 2.3 for etanercept 50 mg twice weekly, and 1.4 for infliximab 5 mg/kg. For serious noninfectious, serious infectious, and malignant adverse events, the estimated NNH was at least 2 orders of magnitude greater and several orders of magnitude greater for events of serious toxicity. The number of patient-years of observation necessary to detect an event was 56 to 73 for serious infection, 164 to 507 for malignancy excluding skin cancer, and 818 to 1286 for congestive heart failure.

**Conclusions:** The likelihood of treatment success for these TNF agents far exceeds the likelihood of serious harm.

**Reviewer’s Comments:** I always run through the litany of risks of these drugs with patients. It is reassuring to be able to tell them that typically one might expect to have to wait a millennium, for example, for any likelihood of drug-related congestive heart failure to be observed in any given patient (although that somewhat misrepresents the meaning of the statistic). (Reviewer-David L. Swanson, MD).

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Keywords: Etanercept, Infliximab, Adalimumab

Print Tag: Refer to original journal article
Renal Stenting Improves Renal Function in Severe Renal Insufficiency

One Year Clinical Outcomes of Renal Artery Stenting: The Results of ODORI Registry.
Sapoval M, Tamari I, et al:
Cardiovasc Intervent Radiol 2010; 33 (June): 475-483

In patients with atherosclerotic renal artery stenosis, renal stenting may result in improvement in hypertension and renal function as long as the patient is stage 3 or below (glomerular filtration rate >30 mL/min/1.73 m²).

Background: Renal stents are placed in renal arteries frequently for renal revascularization to decrease hypertension or to increase renal function in the presence of a significant stenosis. The efficacy and long-term clinical benefits are unclear.

Objective/Design: To present the results of the authors’ prospective, multicenter study on the Tsunami stent placed for hypertension and/or renal function in patients with atherosclerotic renal artery stenosis.

Methods: In 36 institutions, the ODORI registry was used to enroll patients. There were 12 centers. The primary endpoint was acute technical success of producing a <30% residual stenosis. Secondary endpoints included complications, restenosis, improvement in blood pressure, and renal function. Follow-up and ultrasound surveillance was performed.

Results: There were 251 patients enrolled. In 100% of patients, there was technical success. Eighty percent were treated for hypertension and 39% for renal salvage. Combined problems were seen in 25% of patients. A total of 277 stents were used to treat 276 lesions in 221 patients. There was migration of the stent in 1 patient and dissection of the artery in another. There was 1 peri-procedural stent thrombosis resolved by giving thrombolytics. There were 6 additional minor complications periprocedurally that all resolved without intervention or permanent sequelae. One death occurred, causing a 0.5% mortality rate. At 6-month follow-up, 4 patients died, only 1 from renal failure. There was only 1 patient who had a restenosis and required a repeat procedure. At 12-month follow-up, 7 more patients died, with 2 dying from renal failure. One other patient had a repeat procedure because of restenosis. As for control of hypertension, there was a statistically significant drop from a mean blood pressure of 171/89 down to a mean of 142/78 at 6 months and a mean of 140/80 at 12 months. The glomerular filtration rate improved only slightly or worsened in patients with values <30 mL/min/1.73 m²; however, it improved significantly in patients who had values >30 (stages 1 to 3).

Reviewer's Comments: Catheter-based therapy is standard treatment for atherosclerotic renal hypertension. In the literature, the benefit from this therapy was still questioned. In this study, patients’ blood pressure was controlled, as well as the mean pulse pressure, which is shown to be an important predictor of mortality. The improvement in renal function was not as uniform, and it seems that renal stenting appears to stabilize renal function and prevent further deterioration and with that, improving outcome as well as decreasing mortality and the potential for sequelae of renal failure. This study demonstrates that the Tsunami stent functioned well in this multicenter study for up to 12 months of follow-up. There was a great success rate with a low complication rate. (Reviewer-Sharon Gonzales, MD).

© 2010, Oakstone Medical Publishing
Keywords: Renal Artery Stenting, Revascularization, Renal Insufficiency, Renovascular Disease

Print Tag: Refer to original journal article
Antibiotic use is associated with subsequent isolation of resistant bacteria from respiratory and urinary tracts of individuals.

**Background:** There is an established relationship between prescribing patterns and antibiotic resistance at the population level. Less is known about the effects of prescribing patterns on antibiotic resistance in individual patients.

**Objective:** To examine the relationship between antibiotic administration and antibiotic resistance in individual patients.

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

**Methods:** Online publication databases were searched for observational and experimental studies examining the relationship between the prescription of antibiotics in primary care and the measure of antimicrobial resistance. Studies were included if they reported quantitative measures of antibiotic resistance in individuals who were prescribed antibiotics in primary care. The outcome measure was the odds ratio (OR) or relative risk (RR) of antibiotic resistance in patients exposed to antibiotics compared to those not exposed to antibiotics.

**Results:** 4373 potential studies were identified and reviewed; a total of 24 studies were included: 5 randomized controlled trials and 19 observational studies (2 prospective and 17 retrospective). These studies included 15,505 adults and 12,103 children. All studies were performed in countries where antibiotics were available by prescription only. Twenty-two studies were of patients with symptomatic infection, and 2 studies involved asymptomatic healthy volunteers. The odds of urinary bacterial antibiotic resistance were significantly increased at all time points measured in 5 studies: 0 to 1 month (OR, 4.40); 0 to 3 months (OR, 2.48); 0 to 6 months (OR, 2.18); and 0 to 12 months (OR, 1.33). In a prospective study of patients with symptomatic respiratory infection, the RR of isolation of resistant *Haemophilus* isolates was 1.9 in patients who received antibiotics 2 weeks postexposure, but decreased to 1.0 at 12 weeks postexposure. Interestingly, a meta-analysis of antibiotic use did not find an association between antibiotic prescription within the previous 12 months and the prevalence of methicillin-resistant *Staphylococcus aureus*.

**Conclusions:** Antibiotic use is associated with the subsequent isolation of resistant bacteria from respiratory and urinary tracts of individuals. These effects wane over time but can be detected in some cases as much as 1 year after antibiotic use.

**Reviewer's Comments:** This is a powerful cautionary tale. This paper provides compelling evidence that antibiotic use has very real consequences for individual patients. This provides further ammunition for efforts to limit antibiotic use to individuals in whom there is a real indication and a clear benefit. (Reviewer-Paul R. Sutton, PhD, MD).

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Keywords: Antibiotic Resistance, Primary Care

Print Tag: Refer to original journal article
Probiotics to Treat Mastitis?

Treatment of Infectious Mastitis During Lactation: Antibiotics Versus Oral Administration of Lactobacilli Isolated From Breast Milk.

Arroyo R, Martín V, et al:

Clin Infect Dis 2010; 50 (June 15): 1551-1558

In women with lactational mastitis, oral administration of 2 lactobacillus species reduced symptoms of mastitis, recurrence rate, and bacterial colony counts more than did antibiotic therapy.

Background: Mastitis is a common infection in lactating women and a common reason to stop breastfeeding. Standard therapy includes antibiotics to cover usual causative organisms (Staphylococcus aureus, S epidermidis, Streptococcus, or Corynebacterium species) and frequent nursing. The authors of this study, looking for alternate ways to treat and prevent mastitis, have previously isolated potentially probiotic strains of lactobacilli from the milk of healthy mothers.

Objective: To evaluate the efficacy of these strains of lactobacilli in treating lactational mastitis.

Design: Randomized controlled trial.

Participants: 352 Spanish women with mastitis, which was defined as having breast inflammation, painful breastfeeding, and both elevated bacterial colony count and leukocyte count in the milk.

Methods: Volunteers with acute mastitis were assigned to 1 of 3 groups. The first group received whichever antibiotic was prescribed by the primary midwife and no probiotics. The second and third groups received no antibiotics; probiotic group A received a daily capsule of a freeze-dried Lactobacillus fermentum strain, and probiotic group B received an L salivarius strain. Symptoms were assessed with a 0 to 10 breast pain score, and milk samples were collected on days 0 and 21.

Results: At baseline, all 3 groups had similar bacterial colony counts in milk. S epidermidis was isolated from 73% of baseline samples, S aureus in 43%, Streptococcus mitis in 30%, and lactobacilli in 0%. By day 21, mean colony counts were lower in all 3 groups but were significantly lower in the 2 probiotic groups than in the antibiotic group. At day 21, lactobacilli were isolated from more than half of milk samples of the probiotic groups but from none of the antibiotic group. By day 21, the breast pain score had improved in most women; in probiotic groups, 85% had recovered completely, and the remainder had slight pain with breastfeeding. Clinical symptoms in the antibiotic group varied more and depended on the antibiotic given, improving most in those treated with cotrimoxazole and amoxicillin-clavulanate and least in those given cloxacillin and erythromycin. At 3 months, the rate of recurrent mastitis was 30% in antibiotic groups and 10% in probiotic groups. Nine percent of women treated with antibiotics had stopped breastfeeding versus none of those given probiotics.

Conclusions: These 2 strains of lactobacilli may be alternatives to antibiotics for treatment of lactational mastitis.

Reviewer's Comments: I was pulled in by the headline, and read the whole article hoping to find out how the heck freeze-dried lactobacilli ended up in breast milk. No luck -- "further studies are required to elucidate the pathways that lactobacilli may follow to colonize the mammary gland." This is nonetheless pretty interesting, although not yet ready for prime time (first we need another few studies and a source of human milk lactobacillus capsules). This is another example of how antibiotics may not be the best answer for many common problems. (Reviewer-Karen A. McDonough, MD).

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Keywords: Lactation, Mastitis, Lactobacillus

Print Tag: Refer to original journal article
Can Women Screen Themselves for Cervical Cancer?

HPV Testing on Self Collected Cervicovaginal Lavage Specimens as Screening Method for Women Who Do Not Attend Cervical Screening: Cohort Study.

Gök M, Heideman DAM, et al:

BMJ 2010; 340 (March 11): c1040

Self-sampling for cervical cancer screening is a feasible and effective alternative adjunct to large, population-based programs.

Background: The practice of cervical cancer screening is changing rapidly, with emerging technologies that are primarily based around human papillomavirus (HPV) detection. This study from the Netherlands looks at the potential effectiveness and findings of self-collected samples.

Objective: To determine response rates to screening through self-collection of cervicovaginal specimens, to examine the validity of specimens, and to identify specific cytologic abnormalities found.

Participants/Methods: A cohort of 28,073 women were identified through the Dutch national cervical cancer screening program as being nonresponders to 2 requests to attend conventional pap cytology screening; 27,792 women were randomly assigned to self-sampling, and 281 were assigned to receive a third request for conventional screening. A Delphi Screener kit was sent for collection of specimens. Women found to be positive for high-risk HPV were referred for physician evaluation, and those with abnormal cytology were referred for colposcopy. Those with normal findings had repeat follow-up in 1 year.

Results: 7404 (27.5%) women responded with self-sampling compared to 51 (16.6%) of the repeat reminder-only group; 99.8% of samples collected were valid for high-risk HPV testing, and 10.3% were positive for high-risk HPV. On subsequent follow up, almost one third of these cases were confirmed to be positive, and 99 (1.3%) were found to have cervical intraepithelial neoplasia grade II (CIN II) or higher-grade lesions. When comparing women who had not previously responded to those who had, there was a significantly higher risk of having CIN II or higher grades of cervical pathology.

Conclusions: Self-sampling for cervical cancer screening is a feasible and effective alternative adjunct to large, population-based programs.

Reviewer's Comments: This large cohort study effectively demonstrates a "proof of concept": that women will respond to offers for screening through self-sampling and that specimens are indeed usable and have reasonable yield for target pathology. In addition, the study shows that women who sent in self-collected samples were very compliant with follow-up visits in person. Those who had missed screening in previous years were more likely to have higher grades of cytopathology, suggesting that this sampling technique could effectively capture women who were previously resistant to the idea of attending an office visit for a pelvic exam. However, a rather extensive database and infrastructure are required to determine which women are eligible to participate, and to track follow-up. In this Netherlands cohort, screening rates were effectively improved from 65.0% to 70.2%, and CIN II or higher pathology was detected in 1.3% of the population instead of only 0.8%. One of the more exciting implications of this study is its potential impact on large populations of women in developing countries. (Reviewer-Emily Y. Wong, MD).

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Keywords: Cervical Cancer Screening, High-Risk Human Papillomavirus, Cervical Intraepithelial Neoplasia

Print Tag: Refer to original journal article
Candidate genes identified in this study for preferential antidepressant response of serotonergic versus noradrenergic medication continue to point to neurogenesis and inflammatory responses in depression.

**Background:** A systematic exploration of variation across the genome has the potential to detect genetic variants that may help in understanding the biology of antidepressant action, and better guide specific antidepressant selection in an individual patient with a greater likelihood of efficacy.

**Objective:** To report the findings from a genome-wide pharmacogenetic analysis of >500,000 common genetic variants. These variants were tested for association with a change in depression severity over a 12-week period after treatment with a serotonergic or noradrenergic antidepressant among subjects with moderate to severe depression.

**Methods/Participants:** The Genome-Based Therapeutic Drugs for Depression was a 12-week partially randomized open-label pharmacogenetic study with 2 active treatment arms. A total of 706 patients were included in the main analysis. The primary outcome measure was the 10-item Montgomery-Åsberg Depression Rating Scale. DNA was extracted and assayed for >610,000 single nucleotide polymorphisms and copy number variant markers. Participants were then randomized to treatment with either escitalopram or nortriptyline; there was no placebo group. Statistical analyses were conducted to determine if there were associations between genotype and outcome in subjects treated with escitalopram and in those treated with nortriptyline.

**Results:** Regardless of which antidepressant was used, the outcome of treatment was associated with polymorphisms in 2 regions on chromosomes 1 and 10. The findings also showed that some previously unexpected regions might be more potent predictors of antidepressant response than functional candidate genes. For example, the uronyl-2-sulphotransferase gene, which is essential for neurogenesis and neuronal migration, was found to be specific to nortriptyline response. The apparent delayed onset of the pharmacogenetic effect on response after 4 weeks of treatment was consistent with a neurogenesis-related mechanism. For escitalopram, the marker for interleukin (IL)-11 was found to have a suggestive level of significance for escitalopram responders. This finding is consistent with the role of inflammation in a subtype of depression and could explain the specific moderation by cytokines IL-6 and IL-11 of response to escitalopram.

**Conclusions:** A candidate gene involved in neurogenesis has been identified for the antidepressant efficacy of nortriptyline, although this finding requires replication.

**Reviewer’s Comments:** Pharmacogenomic studies will change prescribing practices in the future. It is conceivable that genotyping individuals for specific, as yet unidentified, markers will help guide antidepressant selection. This may be a bold new frontier in psychiatry. (Reviewer-John G. Koutras, MD).

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Keywords: Genetic Scanning, Selective Serotonin Reuptake Inhibitors, Noradrenergic

Print Tag: Refer to original journal article
Topical Capsaicin Effect Varies by Ethnicity

Ethnic Differences in Pain, Itch and Thermal Detection in Response to Topical Capsaicin: African Americans Display a Notably Limited Hyperalgesia and Neurogenic Inflammation.

Wang H, Papoiu ADP, et al:

Br J Dermatol 2010; 162 (May): 1023-1029

Post-capsaicin warmth thresholds increase for African Americans and decrease in Hispanics, who also experience increased pruritis.

Background: One of the most useful spinoffs of the genomics revolution over the past decade has been an increased understanding of the polymorphisms that determine response to therapeutic drugs. There are personal as well as ethnic differences in response to medications—in fact, we’ve learned to expect them. One drug that shows a significant variation in effectiveness from person to person is capsaicin, an analgesic drug used for treatment of pain, including pain from peripheral neuropathy.

Objective: To evaluate ethnic variations in noxious stimulus detection after treatment with topical capsaicin.

Participants: 40 healthy subjects: 10 African Americans, 10 East Asians, 10 Hispanics, and 10 Caucasians. None of the individuals except 1 Hispanic subject was reported to consume a large amount of chili peppers.

Methods: The authors measured warmth sensation and heat pain detection thresholds and pain intensity before and after application of capsaicin or placebo on the forearms. The device used was a standard commercial quantitative thermosensory testing system. This system uses a 12 cm2 probe that warms the skin at a rate of 0.4°C per second up to 50°C. Subjects reported a warmth sensation threshold followed by a heat pain detection threshold. Pain was also reported after capsaicin or placebo application using a 0 to 100 pain intensity scale. Any nonpainful sensations were also recorded. Investigators measured skin blood flow with a laser Doppler device, and any positive skin flare response was measured visually with a ruler.

Results: In African Americans, the heat pain detection threshold, pain intensity, and skin blood flow did not change significantly after capsaicin application. However, in the other 3 groups, there was significant hyperalgesia and vasodilatation. The post-capsaicin warmth sensation threshold increased in African Americans and decreased in Hispanics. Hispanics also uniquely experienced post-capsaicin itch.

Conclusions: African Americans displayed significantly reduced pain hypersensitivity after topical capsaicin compared to the 3 other ethnic groups.

Reviewer’s Comments: Several previous studies have shown differences in pain thresholds among ethnic groups, with most suggesting that African Americans generally have a decreased tolerance to pain stimuli, a lower thermal pain tolerance, and higher ratings of unpleasantness and intensity to thermal stimuli compared to Caucasians. This study showed that topical application of capsaicin was an exception. Although African Americans had no change in heat pain detection, the warm sensation threshold was increased. Therefore, this study still begs the question of whether capsaicin would be a more useful drug in African Americans for neuropathic pain and itch than in other ethnic groups; it certainly suggests it would be better tolerated. Until there is further study, since capsaicin is safe, it seems reasonable to offer it as an optimistic therapeutic choice, especially for African Americans. (Reviewer-David L. Swanson, MD).

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Keywords: Capsaicin, Pain, Ethnicity, Neuropathy

Print Tag: Refer to original journal article
Intensive internet use may reflect a distinct condition, but scaled endorsement of use is highly correlated with depression and suicidality, making consideration of internet addiction as a unique disorder likely to remain an area of controversy.

**Background/Objective:** Problematic, intense, compulsive use of the internet, or internet addiction, has been getting attention for consideration as a distinct disorder as the content for DSM-V evolves. Areas of high internet use, such as South Korea and China, with China having the largest volume of broadband use in the world, have identified this emerging syndrome as a public health problem, especially among adolescents. Efforts to operationalize and explore the validity of such a label have found wide-ranging prevalence rates (0.9% to 38.0%), which raise questions as to the reliability and consistency in definitions as well as probably a wide variation of such behaviors among different subgroups. In the face of still evolving criteria and understanding of what such criteria might mean in terms of a distinct condition, the study here used serial surveys of adolescents in Hong Kong to look at both the stability of a criteria set to uniquely and independently discriminate, as well as the correlation of such symptoms with others, such as scale-measured depression and anxiety.

**Methods:** A 2-wave household survey of adolescents aged 15 to 19 years included questions regarding suicidality, depression and anxiety (Center for Epidemiologic Studies Depression Scale and Depression Anxiety Stress Scales, respectively), and endorsement of statements as to the frequency, need, and social-occupational impact of use of the internet. It was administered to 511 subjects who were then followed up 1 year later with a 62% follow-up response rate.

**Results:** Of 8 items of queried internet use, 71.6% endorsed 0 to 2 symptoms, 21.6% endorsed 3 to 4 symptoms, and 6.7% endorsed ≥5 symptoms. While scores on internet use items and thresholds were sufficiently statistically discriminated from other measured psychological dimensions, such scoring was highly correlated to comorbid psychiatric conditions, especially suicidality and depression. The square root of the average variance of internet addiction items, a common metric for establishing the discriminating value of a collection of items, was 0.51, which was larger than correlation coefficients of these symptoms with other correlates.

**Conclusions:** While showing marginally discriminant characteristics, internet use symptoms and scaled intensity also significantly varied along measures of suicidality and depression.

**Reviewer's Comments:** The apparent unique behavior of internet use items further supports this as a robustly coherent behavior, but still one that may be primarily driven and sustained when excessive and intrusive by other psychological conditions. Likely, more work to be done to settle what excess surfing means. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

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Keywords: Adolescents, Internet Addiction, Prevalence

Print Tag: Refer to original journal article
Organophosphate pesticide exposure appears to be associated with diagnosis of attention-deficit/hyperactivity disorder.

**Background/Objective:** The developing brain is more susceptible to neurotoxins, therefore placing children at greater risk from pesticide organophosphates. Also, the dose of pesticides per body weight is typically larger for children. Epidemiologic studies linking exposure to organophosphates and neurodevelopment have focused on populations with high levels of exposure, relative to the U.S. population. No studies have addressed possible risks among children with typical levels of exposure. By using data for a representative sample prevalence of U.S. children, this study examines the cross-sectional association between urinary dialkyl phosphate (DAP) metabolite concentrations and attention-deficit/hyperactivity disorder (ADHD) in children aged 8 to 15 years.

**Methods:** The National Health and Nutrition Examination Survey (NHANES) is a population-based health survey that includes questions about demographics and health history, and it also involves collecting blood and urine samples during physical examinations. In those children who carried a diagnosis of ADHD, diagnosis was confirmed by administration of the Diagnostic Interview Schedule for Children IV (DISC-IV). Six urinary DAP metabolites were measured.

**Results:** The study sample included 1139 children aged 8 to 15 years; 119 children meeting criteria for any ADHD subtype. Of the total sample, 93.8% of children had at least 1 detectable DAP metabolite. The odds of meeting DISC-IV criteria for ADHD increased with the total DAP metabolites detected in urine samples. This association was not explained by gender, age, socioeconomic status, race/ethnicity, fasting duration, or creatinine concentration.

**Conclusions:** Children with levels higher than the median of detectable dimethyl thiophosphate concentrations were twice as likely to be diagnosed with ADHD as were those with undetectable concentrations.

**Reviewer’s Comments:** As the authors pointed out, the most important limitation of the present study is the assessment of organophosphate exposure through measurement of DAP metabolites in only 1 spot urine sample. Serial measurements over a longer time would have provided a better assessment of average organophosphate exposure. Also, the authors found a significant association between a specific metabolite and ADHD-hyperactive subtype only (not inattentive or combined types). Since the authors conducted a DISC-IV only on children who were identified as having ADHD prior to the survey, it could be that organophosphate exposure actually increases hyperactive behaviors (similar to certain food dyes) and that these children are then more likely to be identified as having ADHD by teachers and primary care providers. This would result in an underestimation of ADHD in the remainder of the sample. (Reviewer-John G. Koutras, MD).

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**Keywords:** ADHD, Organophosphates Pesticides, Risks, Dialkyl Phosphate, Urinary Metabolites

Print Tag: Refer to original journal article
Computer Games -- Brain Training or Idle Diversion?

Putting Brain Training to the Test.

Owen AM, Hampshire A, et al:

Nature 2010; 465 (June 10): 775-778

Commercial software purports to improve cognitive functioning by repetitive stimulation of memory, pattern recognition, visuospatial processing, and calculation. This study finds little evidence in support of this claim.

Background: Commercially available "brain training" software purports to improve cognitive functioning through tasks that require concentration, memory, calculation, pattern recognition, and hand-eye coordination. There is little scientific evidence to support these claims.

Objective: To assess whether brain training improves general cognitive functioning.

Methods: The authors conducted a 6-week online study of >11,000 participants in the United Kingdom. Subjects were viewers of a BBC science program "Bang Goes the Theory." Subjects were randomized to 1 of 3 groups and asked to perform 6 online tasks for at least 10 minutes a day 3 times a week for 6 weeks: (1) tasks emphasized reasoning, planning, and problem-solving; (2) tasks emphasized short-term memory, attention, visuospatial processing, and mathematics (similar to commercially available software); and (3) tasks consisted of answering obscure questions using any available online resource (control group). Subjects were given a battery of 4 previously validated tests of memory, cognition, and reasoning before and after 6 weeks of online training.

Results: Of >52,000 subjects who initially enrolled, >11,000 completed benchmarking tests before and after training and completed at least 2 online sessions (average number of online sessions, 24.47 over 6 weeks). Participants in each of the 2 intervention groups and the control group showed very small to small improvements in several individual neuropsychological metrics over the 6-week intervention, most consistent with a small test-retest practice effect. By comparison, group 1 intervention subjects showed a large improvement in group 1 online tasks; group 2 intervention subjects showed a large improvement in group 2 online tasks. The improvement in specific online tasks did not translate into improvement in more general measures of memory, cognition, and reasoning. There was no correlation between the number of online training sessions and improvement in validated measures of cognition.

Conclusions: Online "brain training" activities improved performance on specific trained tasks but did not result in generalizable improvement in neuropsychological measures of memory, cognition, and reasoning.

Reviewer's Comments: This very interesting and well-done paper does not support claims that computerized "brain training" software improves cognitive functioning. Not only did online training not substantially improve measures of cognition, but also there was no evidence of a dose-response effect in which more training resulted in greater improvement. Video games may be enjoyable but seem unlikely to improve cognitive functioning. (Reviewer-Paul R. Sutton, PhD, MD).

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Keywords: Video Games, Cognition

Print Tag: Refer to original journal article
Silent pulmonary embolism may be more prevalent in patients aged >70 years and those with proximal deep venous thrombosis.

**Background:** Postmortem reviews suggest that pulmonary embolism (PE) is often unsuspected or undiagnosed. A number of smaller studies have looked at the incidence of asymptomatic (silent) PE, but the prevalence of silent PE has been difficult to estimate.

**Objective:** To determine the prevalence of silent PE in patients with deep venous thrombosis (DVT).

**Methods:** The authors identified 958 citations. Inclusion criteria were as follows: clear description of methodology for diagnosis of PE and raw data on occurrence of silent PE, thus allowing calculation of the prevalence rate. Tier 1 included studies that made diagnosis of silent PE on the basis of pulmonary angiography, CT angiography, or high-probability ventilation perfusion (V/Q) scanning, as defined by the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) criteria. Tier 2 studies identified PEs on the basis of V/Q scans, but either did not use PIOPED criteria or did not specify what criteria were used.

**Results:** 12 Tier 1 and 16 Tier 2 studies were included in the final analysis. Pooled data from the Tier 1 studies found a prevalence of 27% (703 of 2656) for silent PE in patients with DVTs. Pooled Tier 2 studies determined a prevalence of 37% (962 of 2577). Five studies specifically compared patients with proximal and distal DVTs. Those with proximal DVTs were found to have a much higher prevalence of silent PEs compared to those with distal DVTs: 36% (196 of 546) compared to 13% (15 of 113). One study showed that when the DVT extended to the pelvic veins, 50% (69 of 139) of patients had silent PEs. Older patients were more likely to have silent PE: 40% in those aged >70 years compared to 14% in those aged <40 years.

**Conclusions:** Prevalence of silent PE in patients with DVT is approximately one third, based on conservative criteria for the definition of PE.

**Reviewer's Comments:** This study raises an interesting set of questions. Given the relatively high prevalence of DVTs, what would be an effective strategy for identifying patients who might be at higher risk for PE? What role does silent PE play in causing recurrent or even fatal PE? Certainly data in the study suggest that patients with DVTs and silent PEs were much more likely to have a recurrent PE compared to the risk of a first-time PE in patients with DVTs who had never had one. The overall message I came away with was to have an even lower threshold for suspecting PEs, recognizing that they can be and often are silent. It probably makes intuitive sense to be more suspicious in older patients and those with large proximal DVTs, but obviously CT angiograms are not without risk, and V/Q scans can be problematic to interpret. (Reviewer-Emily Y. Wong, MD).
Can Equality Be Achieved Through QI Programs?

Racial and Ethnic Differences in the Treatment of Acute Myocardial Infarction: Findings From the Get With the Guidelines-Coronary Artery Disease Program.

Cohen MG, Fonarow GC, et al: Circulation 2010; 121 (June 1): 2294-2301

Quality improvement programs directed at evidence-based acute myocardial infarction care can decrease or eliminate care differences between racial/ethnic groups.

**Background:** Multiple studies have demonstrated that racial and ethnic minorities are less likely to receive evidence-based cardiovascular care. Studies have also shown that quality improvement (QI) programs can improve hospitals’ adherence to guidelines and improve short- and long-term patient outcomes. There are not enough data on whether implementation of QI programs affects racial and ethnic differences in care. **Objective:** To determine if racial/ethnic differences in evidence-based acute myocardial infarction (MI) care “persist among hospitals participating in a national QI program.”

**Methods:** Get With the Guidelines is an observational registry and QI program established by the American Heart Association. It includes 548 hospitals with a database of almost 300,000 patients treated for acute coronary syndromes from 2000 to 2007. Data on >140,000 patients from >440 hospitals with appropriate data on race/ethnicity were used for this analysis. Performance measures for acute coronary syndromes were identified, including a summary of "defect-free" care. Performance measures included use of aspirin, β-blockers, lipid-lowering therapy, angiotensin-converting enzyme inhibitors in appropriate patients, and counseling on smoking cessation, as well as time to open artery for those with ST-elevation MI. Patients were categorized as white, black, or Hispanic.

**Results:** Data from 2002 to 2007 were included, and adherence to performance measures was assessed for each year. In the beginning of the study period, there were significant differences between racial/ethnic groups in both how quickly percutaneous coronary intervention was performed and how quickly thrombolytics were given, as well as in medical treatment. During the study, 49.4% of white patients had a door-to-balloon time of <90 minutes, while 38.1% of blacks and 41.0% of Hispanics achieved this goal. In the first 2 years of the study, blacks were 27% to 41% less likely to receive "defect-free" care than whites; this difference did not exist by the end of the study period.

**Conclusions:** For hospitals enrolled in a QI program for acute MI, evidence-based care improved over time. Despite initial differences in care based on race/ethnicity, implementation of QI programs reduced or eliminated these gaps in care.

**Reviewer's Comments:** For diseases such as acute coronary syndromes for which there are ample data and guidelines to guide effective treatment, seemingly algorithmic QI programs are an appealing way to ensure that patients receive appropriate treatments. This study nicely demonstrates that such programs also help mitigate differences in care based on race/ethnicity. For hospitals considering adopting such programs, this study may provide additional data needed to justify the expense and culture shift necessary to implement these programs. Notably, however, there remain differences in percutaneous coronary intervention/thrombolytic timing that need continued attention. (Reviewer-Karen Stout, MD).

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Keywords: Acute Myocardial Infarction, Racial/Ethnic Differences, Guideline-Based Care

Print Tag: Refer to original journal article