Sertraline appears to be superior to other newer-generation antidepressants in terms of efficacy and tolerability, but mirtazapine appears to be the most efficacious.

**Objective:** To conduct a multiple treatment meta-analysis (a network meta-analysis) to integrate data from direct antidepressant comparison studies and to compare the efficacy of 12 new-generation antidepressants. In addition, indirect comparisons were made between trials by combining results of efficacy when compared with a common comparator treatment. Data were analyzed for comparative efficacy among antidepressants and for adverse effects.

**Methods:** The analyses included only randomized, controlled trials that used monotherapy with any of the selective serotonin reuptake inhibitors (SSRIs), bupropion, mirtazapine, duloxetine, or venlafaxine. Remission was defined as at least a 50% improvement from baseline score on the Hamilton Depression Rating Scale, Montgomery-Asberg depression rating scale, or scores of "improved" or "very much improved" on the clinical global impression (CGI) scale at 8 weeks. The analyses were conducted on both the number of patients who responded to the treatment and the number of patients who dropped out. Overall, 117 studies met the inclusion criteria, which included a total of 25,928 subjects. Only 23 trials were 3-arm trials involving 2 active comparators and placebo. The synthesized data were then compared with sophisticated random effects models to determine efficacy and tolerability differences among the various antidepressants, using fluoxetine as the reference drug for efficacy.

**Results:** The outcomes demonstrated that escitalopram was more efficacious than citalopram. Escitalopram, mirtazapine, sertraline, and venlafaxine demonstrated superior efficacy over the other SSRIs and serotonin noradrenaline reuptake inhibitors (SNRIs). In terms of tolerability, escitalopram, sertraline, bupropion, and citalopram were better tolerated than the other antidepressants.

**Conclusions:** Escitalopram and sertraline demonstrated superior efficacy and tolerability.

**Reviewer’s Comments:** Mirtazapine and venlafaxine, both antidepressants with serotonin and norepinephrine mechanisms of action, demonstrated superior efficacy in this meta-analysis of 12 new-generation antidepressants. Duloxetine, another dual-action agent, was toward the bottom of the group of antidepressants for both tolerability and efficacy. Unfortunately, mirtazapine and venlafaxine were not in the better-tolerated group of medications. For the best of both worlds (tolerability and efficacy), the results of this meta-analysis point to escitalopram and sertraline. (Reviewer-John G. Koutras, MD).

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**Keywords:** Antidepressants, Efficacy, Tolerability

**Print Tag:** Refer to original journal article
The World Health Organization predicts that depression will be the second highest disease burden worldwide by 2030. Surprisingly, twice-weekly exercise for 4 months did not have a significant effect on clinical severity.

**Background:** Theory would predict that aerobic exercise and strength training could improve depressive symptoms by increasing endorphin levels, serotonin activity, or neurotrophic factors. Exercise increases cognitive functioning in animal studies, and small human clinical trials have demonstrated increased benefits for depressive symptoms with increasing exercise intensity.

**Objective:** To compare the benefits and risks of strength training, aerobic training, and relaxation training in individuals with major depression.

**Methods:** All participants (age range, 18 to 55 years) met ICD-10 criteria for depression. Important exclusion criteria included suicide risk, substance abuse, or regular exercise. Participants were randomly assigned to receive strength, aerobic, or relaxation training and were further randomized based on their medication status (no antidepressants, antidepressants for <6 weeks, or antidepressants for >6 weeks). The training sessions were 90 minutes each twice a week for a total of 32 sessions. Participants were assessed at 4 and 12 months with the primary outcome of the Hamilton Rating Scale for Depression.

**Results:** 55 participants were randomly assigned to each exercise group. Differences in maximal oxygen uptake and repetition maximum for knee extension, chest press, and leg press indicated that both the strength and aerobic exercise groups increased their respective physical parameters. There were no significant differences between the 3 groups in terms of improvement in depression score or effect of antidepressant medication history. There were also no significant differences in terms of cognitive functioning across the 3 groups. The only significant finding was that strength training significantly reduced days absent from work at 12 months.

**Conclusions:** Exercise for 4 months did not have a significant effect on clinical depression severity, either at the end of the exercise intervention or 8 months later.

**Reviewer's Comments:** I wanted this trial to demonstrate that exercise can treat depression. Unfortunately, the results did not support that theory. There were limitations to the study that could have produced the negative findings, such as exercise interventions only 1 to 2 times per week and using medicated and nonmedicated individuals. However, it is also possible that exercise is a transient mood elevator that works for only a short time after the exercise. Despite this research, I am still going to recommend exercise for my patients, both for physical and mental health benefits. (Reviewer-Elizabeth Ford, MD).

© 2009, Oakstone Medical Publishing

Keywords: Depression, Exercise, Management

Print Tag: Refer to original journal article
Menopausal HT Increases Ovarian Cancer Risk

Hormone Therapy and Ovarian Cancer.
Mørch LS, Løkkegaard E, et al:
JAMA 2009; 302 (July 15): 298-305

All forms of menopausal HT, even vaginal estrogen, increase the risk of a new ovarian cancer diagnosis.

Background: Several studies have demonstrated increased risk of ovarian cancer in women using menopausal hormone therapy (HT), but the differences in types, routes, doses, and formulations have not been defined.

Objective: To determine the risk of ovarian cancer with different types of postmenopausal HT.

Design/Participants: Prospective, observational, cohort study from 1995 to 2005 of all women in Denmark aged 50 to 79 years, linking information in national registries including the cancer registry and prescription database. Women who had had bilateral oophorectomy or any cancer potentially sensitive to hormones were excluded, leaving 909,946 women who were followed up, on average, for 8 years (7.3 million women-years).

Results: 3068 new ovarian cancers were diagnosed during the study. Compared with never-users of HT, current users had a 38% higher risk of ovarian cancer (RR, 1.38; 95% CI, 1.26 to 1.51). The risk after discontinuation of HT declined to that of never-users in only 2 to 4 years off of HT. The risk was slightly higher with cyclic rather than continuous regimens and was highest for those on long cycles (RR, 2.05; 95% CI, 1.44 to 2.93). Risk seemed slightly higher with estrogen plus progestin compared with estrogen alone and with oral compared with transdermal or vaginal estrogen, but the differences between these groups were not statistically significant. Estrogen dose did not affect risk. Too few women in this study used a levonorgestrel intrauterine device, raloxifene, or conjugated estrogens for the risk with these methods to be determined.

Conclusions: Current HT use and recent HT use within the past 2 to 4 years is associated with increased risk for a new diagnosis of ovarian cancer. All forms of HT are associated with increased risk (including vaginal estrogen), but long cycles of combination HT convey the highest risk. This study found an absolute risk increase of 0.12 cases per 1000 woman-years, meaning that 1 extra case of ovarian cancer occurs among 8300 women taking HT for 1 year.

Reviewer's Comments: The wealth of national registry data and the duration of observation were significant strengths of this study, which adds these new findings: (1) even vaginal estrogen is associated with increased ovarian cancer risk; (2) long-cycle HT may convey the highest risk; and (3) the increased risk abates within 2 to 4 years off of HT. While the absolute increase in risk of ovarian cancer from HT is small, the disease is highly morbid (and often fatal). This increased risk should be among the multiple considerations physicians weigh when counseling patients about HT. (Reviewer-Eliza L. Sutton, MD).

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Keywords: Postmenopausal Hormone Therapy, Ovarian Cancer

Print Tag: Refer to original journal article
Venlafaxine, paroxetine, and gabapentin reduce hot flashes in ≥50% of women regardless of breast cancer history or tamoxifen use.

**Background:** Medical management of hot flashes has been an area of intense interest following publication of results from the Women's Health Initiative that demonstrated risks associated with hormone replacement therapy.

**Objective:** To assess the effectiveness of the newer antidepressants and gabapentin in relieving hot flashes.

**Design:** Individual patient-pooled meta-analysis of published randomized, placebo-controlled trials.

**Participants:** 748 patients on antidepressants (417 breast cancer patients, 295 on tamoxifen) and 450 on gabapentin (358 breast cancer patients, 252 on tamoxifen).

**Methods:** Data were compiled from 10 published trials (antidepressants, 7; gabapentin, 3). Baseline hot flash diary data were compared with data from week 4 or 6 on the study drug. Various doses (mg/day) of the venlafaxine, fluoxetine, paroxetine, sertraline, and gabapentin were evaluated.

**Results:** Study drugs were more effective than placebo in reducing hot flashes in all studies, although 95% confidence intervals crossed zero in all sertraline trials and in 2 of 4 paroxetine dose groups (12.5 and 20 mg/day). All study drug patient groups except 1 (sertraline 50 mg/day in 1 study) experienced a ≥50% reduction in hot flashes in at least half the patients, while only 2 of 11 placebo groups had similar reductions. The placebo group had a mean 24% reduction in hot flashes. The relative mean number of hot flash score reductions for these study drugs compared with placebo were: venlafaxine, 33% (75 mg); paroxetine, 13% to 41% (10 to 25 mg); fluoxetine, 13% (20 mg); sertraline, 9% to 18% (50 mg) and 3% (100 mg); and gabapentin, 35% to 38% (900 to 2400 mg). Results were not altered by considerations of sample size. Hot flash scores and hot flash frequency results were interchangeable. Analyses demonstrated no impact from factors such as age, race, breast cancer history, or tamoxifen use.

**Conclusions:** The newer antidepressants and gabapentin are effective in reducing hot flashes in women, and venlafaxine, paroxetine, and gabapentin are more effective than sertraline or fluoxetine.

**Reviewer’s Comments:** This analysis makes a strong case for the use of these drugs in hot-flash management. Side effects and cost are important considerations.  (Reviewer-Alan B. Grosbach, MD).
Does Mammography Find Too Many Breast Cancers?


Jørgensen KJ, Gøtzsche PC:

BMJ 2009; 339 (b2587):

While breast cancer screening has been shown to reduce the death rate from breast cancer, 25% to 33% of the breast cancers identified by mammographic screening and treated would never have become clinically apparent.

**Background:** Some cancers found by screening and then treated would never have caused significant future health problems. These cancers are considered to have been "overdiagnosed."

**Objective:** To estimate the rate of breast cancer overdiagnosis from widespread mammographic screening.

**Design:** Systematic review of data on the incidence of breast cancer for 7 years before and 7 years after implementation of population-based mammographic screening.

**Methods:** Through a literature search, the authors identified 5 published studies with pertinent data; all studies were in areas with largely white populations (United Kingdom, Sweden, and regions of Canada, Australia, and Norway). Incidence data before screening were extrapolated for women in the age groups screened and for women too young and too old for screening. The increased diagnosis rate among screened women was compared with subsequent change in diagnosis rates among older women. An increase due to screening not matched by a subsequent decrease in older women was considered to reflect overdiagnosis. Incidence data among women too young for screening served as a marker of the change in the baseline incidence over time in each community.

**Results:** In 3 of the 5 regions, the incidence rate did decrease in older women in the years after screening became widespread, but nowhere did that decline match the significant increase in incidence in the screened women. In a meta-analysis of the data, the ratio of cases of invasive breast cancer identified during screening to those that would have become clinically apparent in future years without mammographic screening was 1.35 (95% CI, 1.29 to 1.42). With inclusion of carcinoma in situ, the ratio increased to 1.52 (95% CI, 1.46 to 1.58).

**Conclusions:** 1 in 4 invasive breast cancers diagnosed and treated as a result of mammography screening programs would not have been detected clinically in subsequent years. That ratio increases to 1 in 3 when carcinomas in situ are included.

**Reviewer's Comments:** It seems intuitively obvious that every cancer and precancer found and treated because of screening means that person's life has been "saved." This is demonstrably untrue for many cancers, including prostate, lung, neuroblastoma, and now breast. Screening readily finds slower-growing, less-aggressive cancers, leading to overdiagnosis. Treatment of these overdiagnosed subclinical cancers and precancers worsens, rather than improves, the health of overdiagnosed individuals. However, until we can distinguish between the cancers that pose future risk to health and those that do not, we should continue screening measures shown to improve overall mortality, avoid those that do not, and inform the public about the uncertainty involved. (Reviewer-Eliza L. Sutton, MD).

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Keywords: Mammography Screening Programs, Overdiagnosis

Print Tag: Refer to original journal article
Female gender, multiple office visits, and polypharmacy predispose to inappropriate medication prescribing among the elderly.

**Background:** Inappropriate medication prescribing remains a significant problem for the elderly.

**Objective:** To compare the prevalence of inappropriate medication prescribing using electronic health records and to identify the characteristics of those elderly patients with an inappropriate medication on their active medication list.

**Design:** Cross-sectional study.

**Participants:** 61,251 patients >65 years of age (mean age, 76 years) from 2 ambulatory clinics in the United States.

**Methods:** The active medication list consisted of prescription orders either as a new prescription or a refill, as well as over-the-counter medications and herbal preparations as reported by patients and recorded in the electronic health records. Inappropriate medications were classified using the 2002 Beers list and the 2001 Zhan criteria.

**Results:** In both centers, approximately 23% of the patients were taking inappropriate medications as defined by the Beers criteria. Sixteen percent of patients in 1 center had inappropriate medications according to the Zhan criteria compared to 17.3% in the other center ($P < 0.001$). Eight medications were the most commonly prescribed inappropriate medications, of which fluoxetine (4.1% vs 1.5% at centers 1 and 2, respectively) and propoxyphene (5.7% vs 2.3% at centers 2 and 1, respectively) were the most prescribed in both centers. Factors associated most significantly with inappropriate medication prescribing were polypharmacy (>5 medications) in 74% to 79% of patients, female gender (67% of patients), and multiple visits to the primary care clinic (4.3 to 5.8 per year).

**Conclusions:** There are certain factors that predispose to inappropriate medication prescribing, while there is a subset of 8 different medications that account for the majority of those inappropriately prescribed medications.

**Reviewer's Comments:** The main strength of this study was the use of data obtained by electronic health records rather than from surveys or administrative claims or pharmacy-dispensing records. These resources have important limitations regarding underreporting and biases toward patients with continuous health coverage. It was encouraging to see that only 8 medications were responsible for the inappropriate prescribing. Therefore, targeting efforts to avoid these medications would be relatively straightforward. (Reviewer-Norman G. Egger, MD).

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Keywords: Medication Safety, Beers List, Zhan Criteria

Print Tag: Refer to original journal article
Advanced age and multiple comorbid conditions need to be taken into account when recommending screening colonoscopy to elderly patients.

**Background:** The United States Preventive Services Task Force has recently assessed the benefits of screening colonoscopy among older persons and state that, with the competing causes of mortality in older persons, the benefit of colorectal cancer screening will decrease with advancing age. They also do not recommend any type of colorectal screening for persons between 75 and 85 years of age and recommend against screening in persons ≥85 years old.

**Objective:** To describe the risk of adverse cardiac and gastrointestinal events associated with outpatient colonoscopy procedures in older persons.

**Methods:** Medicare claims data from July 2001 to October 2005 were used to assess for adverse events among seniors who had undergone an outpatient colonoscopy and compare these subjects to a similar group who had not undergone the procedure. The study population was limited to seniors between age 66 and 95 years and excluded those who were at a higher risk of perforation from diverticulitis, Crohn's disease, ulcerative colitis, or colorectal cancer. The study was designed to assess for cardiac and gastrointestinal events occurring during the 30 days after the procedure. The matched group of subjects who did not receive the colonoscopy were assigned a "pseudo date" of a procedure that corresponded to a procedure date in those who had received the colonoscopy. The colonoscopy group was assessed based on whether the procedure was performed for screening, diagnosis, or polypectomy.

**Results:** Of the >53,000 procedures included in the analysis, 10% were billed as screening procedures, 33% were diagnostic procedures, and 56% were procedures that involved polypectomy. The risk of perforation was similar for all types of procedures. The risk of bleeding or paralytic ileus was higher among those who had their colonoscopy with a polypectomy compared to the others. The risk of cardiovascular events was higher among those who had a polypectomy and among those who had a diagnostic procedure versus the screening group. The most common cardiac event was an arrhythmia. The risks of a gastrointestinal and a cardiac adverse event increased with increased age. Patients who had colonoscopy and comorbid conditions were at an increased risk of adverse cardiovascular and gastrointestinal events. These comorbid conditions included diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disease, stroke, and heart failure.

**Conclusions:** Older adults are at an increased risk of adverse events associated with colonoscopy. Those with common comorbidities are at a particularly increased risk during these procedures.

**Reviewer's Comments:** Primary care physicians need to take into account the age of the patients and their comorbid conditions when counseling older adults to have a colonoscopy for colorectal screening. (Reviewer-Michael L. Malone, MD).

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Keywords: Outpatient Colonoscopy, Medicare, Adverse Events

Print Tag: Refer to original journal article
Screening men between the ages of 65 and 74 years old for abdominal aortic aneurysm is cost-effective, while rescreening those with normal examinations initially is not.

**Background:** Screening for abdominal aortic aneurysm (AAA) is now covered as part of the" Welcome to Medicare" examination for at-risk patients. Medicare payment guidelines consider the at-risk patient group to be men ≥65 years old who have smoked at least 100 cigarettes in their lifetime. There are no long-term data from a large study on the benefit of 1 screening ultrasound scan.

**Objective:** To assess whether the mortality benefit from screening men aged 65 to 74 years for AAA decreases over time.

**Participants/Methods:** The United Kingdom Multicentre Aneurysm Screening Study (MASS) is a randomized trial of 67,770 men in the United Kingdom. The patients were randomized to receive an invitation for ultrasound screening for AAA (invited group) or not to receive an invitation for screening (control group). A total of 27,204 subjects in the invited group had an ultrasound, and 1334 aneurysms were detected. The patients who had aneurysms between 3 and 4.4 cm were rescanned annually, and those with aneurysms 4.5 to 5.4 cm were rescanned every 3 months. Patients were referred for evaluation for aneurysm surgery if the aneurysm was ≥5.5 cm, if it had expanded by ≥1 cm in 1 year, or if the patient had symptoms related to the aneurysm.

**Results:** Over 10 years of follow-up, 155 deaths due to AAA occurred in the invited group and 296 in the control group (relative risk reduction, 48%; 95% CI, 0.43 to 0.63). The cost per year of life gained was $12,700. Twenty-five of 25,541 patients had a ruptured aneurysm after an initial normal ultrasound scan, with most of these occurring >8 years after screening.

**Conclusions:** The mortality benefit of screening men aged 65 to 74 years for AAA is maintained up to 10 years, and cost-effectiveness improves with time.

**Reviewer's Comments:** This study gives us long-term data on a population screened for AAA. It is a difficult clinical decision, as only a small percentage of those found to have an aneurysm on screening will benefit from surgery. Many more will end up getting repeat ultrasound examinations and may suffer anxiety from it. The risk factors for AAA include male sex, family history of AAA, cigarette smoking, and known peripheral vascular disease. If you decide to screen patients, it is best to screen those with known risk factors. Ultrasound is an excellent test to detect AAA, with a sensitivity of 95% to 100% and a specificity of 100%. Physical examination can be helpful, but only in nonobese patients and only when a careful examination, looking specifically for aneurysm, is performed. (Reviewer-Douglas S. Paauw, MD).

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Keywords: Abdominal Aortic Aneurysm, Mortality, Screening

Print Tag: Refer to original journal article
Having an adequate vitamin D level is associated with less cartilage loss in osteoarthritis.

Background: Of the 25% of people aged >55 years who have knee pain on most days of the month, one half will have changes on x-ray consistent with osteoarthritis (OA). Does vitamin D play a role in cartilage loss that is the hallmark of OA? Prior studies have shown an increased risk of progression of knee OA in those with vitamin D deficiency, but there have been conflicting results when x-ray data were compared.

Objective/Participants: To evaluate 880 residents of Tasmania, aged 50 to 80 years, and to assess serum levels of 25-hydroxyvitamin D (25(OH)D), sunlight exposure, and knee pain by questionnaire.

Methods: MRI of the right knee and plain x-rays of both knees were obtained, allowing quantitation of cartilage volume and assessment of joint space narrowing (JSN) and the presence of osteophytes.

Results: Of the 353 subjects studied initially and again at an average of 2.9 years, 98% were white; the mean age was 61 years, 50% were women, and average body mass index was approximately 28. The data were evaluated, separating out effects of low 25(OH)D on JSN on x-ray in the medial tibial compartment compared to the lateral compartment of the knee; however, low 25(OH)D correlated with loss of cartilage volume on MRI in both medial and lateral compartments of the knee joint.

Conclusions: Vitamin D insufficiency predicted increased knee cartilage loss over the 2.9 years of observation of patients in this study.

Reviewer's Comments: In this study of a relatively homogeneous population in Tasmania, sunlight exposure correlated with 25(OH)D levels, and women with low vitamin D levels at baseline had more knee cartilage loss at the medial more than lateral tibial plateau and were more likely to note knee pain and have OA on x-ray. The addition of MRI information on the quantity of cartilage at the knee is helpful and, more specifically, highlights cartilage as the potential target for vitamin D activity. This study adds to the growing literature identifying low serum vitamin D levels and the risk of developing OA. (Reviewer-Peggy Schlesinger, MD).
Vaccine Refusals Increase Despite School Immunization Requirements

Vaccine Refusal, Mandatory Immunization, and the Risks of Vaccine-Preventable Diseases.

Omer SB, Salmon DA, et al:


Complacency regarding susceptibility and severity of vaccine-preventable diseases and concerns about vaccine safety have led to increased rates of non-medical exemptions from school immunization requirements.

Background: Despite school requirements, deviations from recommended immunization schedules, including vaccine refusals, continue to increase. This trend poses significant risks, both to the individual and the community.

Design: Review of historic and current literature. Discussion: By the early 1980s, the United States legally imposed school immunization requirements, with variations by state. Medical exemptions are currently allowed in all states, religious exemptions are allowed in most, and personal (philosophical) exemptions are permitted in 21 states. In recent years, the rate of nonmedical exemptions has dramatically increased, particularly in states that allow exemptions due to personal beliefs. Because there is marked geographic clustering of nonmedical exemptions, the accumulation of susceptible children in a given area increases the risk of disease outbreaks in that region. Geographic clustering may occur due to characteristics of the local population, opinions of health care providers/community leaders, and local media coverage. Heterogeneity of school policies and attitudes of the school officials responsible for vaccine compliance may also influence exemption rates. As a result, complexity of procedures allowing nonmedical exemptions is inversely proportional to the exemption rate. Studies have demonstrated that measles risk is 22 to 35 times higher in an unvaccinated child.

During recent measles outbreaks, cases have almost universally occurred in unvaccinated individuals—either those with nonmedical exemptions or those too young for vaccination. A case-control study reveals that parents of exempt children are much more likely than those of vaccinated children (51% to 60% vs 15% to 18%) to believe that their children have low susceptibility to vaccine-preventable diseases, that the severity of the diseases is low, and that safety and efficacy of vaccines is low. The most frequent reason for vaccine refusal (in 69%) is concern regarding harmful effects of the vaccine. Primary care providers, including those of unvaccinated children, are cited by parents as the most frequent source of vaccine information, and several studies have highlighted the significant influence of clinicians on parental decisions regarding vaccines. Providers caring for a high proportion of exempt children are less likely to show confidence in vaccine safety and are less likely to perceive vaccines as providing benefit to individuals and the community. The American Academy of Pediatrics encourages clinicians with high confidence in vaccines to continue relationships with families that refuse immunization, and to continue to engage in respectful dialogue to address parental concerns.

Reviewer’s Comments: Ironically, it is precisely because vaccines are so effective at reducing the incidence, morbidity, and mortality of infectious diseases that public perception of the threat of these diseases has changed so drastically. Provisions for personal exemptions to school immunization “requirements” suggest that there is essentially no requirement after all. Without effectively enforced school policies, our ability to control disease outbreaks through the use of vaccines greatly depends on heightened efforts to educate our patients. (Reviewer-Alyssa Siegel, MD).

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Keywords: Vaccine-Preventable Disease, Refusal, Risks

Print Tag: Refer to original journal article
ADHD Medication May Improve Academic Achievement in Elementary School

Positive Association Between Attention-Deficit/Hyperactivity Disorder Medication Use and Academic Achievement During Elementary School.

Scheffler RM, Brown TT, et al:

Pediatrics 2009; 123 (May): 1273-1279

Medication use in children with ADHD appears to be associated with increased academic performance.

Background: Attention-deficit hyperactivity disorder (ADHD) is a common condition in children that is associated with increased levels of inattention, activity, and impulsivity. More than half of affected children are treated with prescription medication that has been proven effective in large trials. Unfortunately, fewer children are treated than would be optimal. Children with ADHD can have poorer school performance than normal children. In the past, research has not shown that academic performance has increased with medication treatment, although some of these studies had methodological issues.

Objective: To examine whether medication use for ADHD contributes to improved academic performance in elementary school.

Design/Methods: This was a retrospective cohort study using data from the Early Childhood Longitudinal study - Kindergarten Class of 1998 to 1999. Data were collected in 5 waves: twice in kindergarten and then once in first, third, and fifth grades. Mathematics and reading achievement was measured by achievement tests paralleling the National Assessment of Educational Progress. The diagnosis of ADHD was reported by parents in the last 4 waves of the study. In the last wave, parents were asked if their children were currently on medication for ADHD. If they were, further information was collected on the length of treatment.

Results: Data were available on 594 children with ADHD. Children who were on medication for their ADHD had an average math achievement score that was 2.9 points higher than that of children who were not receiving medication. Those children with ADHD who were treated for at least 2 waves of the study had an average reading achievement score that was 5.4 points higher than those not treated with medication. Children who had an individualized education program had a less significant association with a higher reading score than those without an individualized education plan. These increased scores in math and reading are equivalent to score gains of 0.2 and 0.3 school years, respectively.

Conclusions: Medication use in children with ADHD appears to be associated with increased academic performance. Children with ADHD who were treated with medication had significantly increased achievement scores in mathematics and reading, especially if treated for longer periods of time. The use of an individualized education plan lessened the impact of medication on reading score improvements. The gains achieved by medication still did not fully compensate for the effect of having ADHD on lowering achievement scores in general.

Reviewer's Comments: There are 2 major points to take home here. First, this is another reason why we should make certain that kids with ADHD receive the recommended medication. Second, this is a stark reminder that, although medication helps children with ADHD normalize their academic performance, they are still at a disadvantage. (Reviewer-Aaron E. Carroll, MD, MS).

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Keywords: ADHD, Medication, Academic Performance

Print Tag: Refer to original journal article
Lower CRP Levels May Lower Risk of Cancer, Death

Baseline C-Reactive Protein Is Associated With Incident Cancer and Survival in Patients With Cancer.

Allin KH, Bojesen SE, Nordestgaard BG:

J Clin Oncol 2009; 27 (May 1): 2217-2224

C-reactive protein may be a potential blood marker to predict risk of heart disease and/or cancer.

**Background:** C-reactive protein (CRP) is an acute phase reactant that is increased during infection, inflammation, heart attack, and perhaps even cancer. CRP is synthesized in the liver after an inflammatory stimulus, which could be a marker of the damage that is caused in the premalignant state or after a diagnosis of cancer. Regardless, the role of CRP and cancer needs further clarification.

**Objective:** To determine the role of CRP in predicting the risk of being diagnosed with and/or surviving cancer in the general population.

**Participants/Methods:** 10,408 individuals with recorded baseline CRP levels from the Danish general population were followed for up to 16 years; >1500 individuals developed cancer, and approximately 1000 died of the disease. Individuals with a cancer diagnosis at baseline were excluded from this analysis.

**Results:** Baseline CRP levels of >3 compared to <1 mg/L were associated with a 30% increase in the risk of cancer of any type, and an 80% increased risk for an early death from cancer. An increased CRP level was associated with an early death in patients with localized disease \( (P = 0.03) \), but not in individuals with metastatic disease. CRP was not associated with the risk of being diagnosed with some cancers, such as prostate cancer, but was more often associated with these cancers in terms of prognosis.

**Conclusions:** Elevated levels of CRP are associated with an increased risk of cancer and an early death from cancer, especially in patients without metastatic disease.

**Reviewer's Comments:** What the heck are we suppose to do with this information?! Should everyone receive CRP or high-sensitivity CRP blood tests during their annual physical? The answer is "yes!" Why not? It is a very cheap blood test and is just a marker of inflammation. This blood test value is generally reduced with better and improved wellness such as exercise, better diet, and reduced belly fat, which is similar to cholesterol. In other words, the risk versus benefit of this blood test seems to favor benefit in most cases. If this test is utilized before or after localized treatment for many cancers, this may also be a good thing because it may be an indicator of adherence to healthy behaviors. (Reviewer-Mark A. Moyad, MD, MPH).

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Keywords: C-Reactive Protein, Cancer, Survival

Print Tag: Refer to original journal article
Unlike those with ST-segment elevation MI, most patients with acute coronary syndrome without ST-segment elevation do not benefit from emergent catheterization or revascularization.

**Background:** Many patients with acute coronary syndrome (ACS) without ST-segment elevation benefit from an invasive strategy, but the optimal timing of intervention is unclear. Early intervention might reduce ischemic events that could occur with delay, but delayed intervention might reduce procedural complications by allowing for plaque stabilization.

**Objective:** To determine the optimal timing of intervention in patients with ACS.

**Participants:** Patients with ACS within 24 hours of symptom onset were randomized to early or delayed intervention.

**Methods:** Inclusion criteria were 2 of the following: age ≥60 years; cardiac biomarker elevation; and ECG evidence of ischemia. Patients randomized to early intervention had angiography as soon as possible and within 24 hours of randomization, while those assigned delayed intervention had angiography after 36 hours. Each group underwent revascularization provided there was at least 1 major coronary artery with a significant stenosis. The primary outcome was a composite of death, new MI, or stroke at 6 months. Secondary outcomes included the composite of death, MI, or refractory ischemia. Prespecified subgroup analysis included use of the Global Registry of Acute Coronary Events (GRACE) score for risk assessment.

**Results:** 3031 patients were randomized, with well matched baseline characteristics. The early and delayed-intervention groups underwent angiography a median of 14 and 50 hours after randomization, respectively. More patients in the early intervention group underwent percutaneous coronary intervention (60% vs 55%), although the rates of bypass surgery were similar (15% vs 14%). The primary outcome was nonsignificantly less in the early intervention group (9.6% vs 11.3%), with no significant differences in death, new MI, and stroke. Secondary outcomes occurred significantly less often in the early intervention group (9.5% vs 12.9%) driven by significantly less refractory ischemia requiring additional intervention. Major bleeding was similar in both groups (3.1% and 3.5%). Subgroup analysis revealed a significant benefit to early intervention in the 33% of patients with the highest risk as assessed by the GRACE score, with a significant reduction in the primary outcome (13.9% vs 21.0%).

**Conclusions:** For most patients with ACS, early intervention does not reduce death, MI, or stroke. However, in the 33% of patients at highest risk, early intervention reduces the primary outcome of death, MI, and stroke. There was no evidence of harm with early intervention.

**Reviewer’s Comments:** For patients with ACS, medical therapy and revascularization reduce the risk of death and MI. This trial suggests that, for most patients who are to undergo angiography, there is no harm to delaying the procedure if, for example, there is no catheterization lab immediately available or the patient is admitted on a weekend. However, for the very high-risk patient, early intervention offers a potential outcome benefit. Therefore, risk stratification and tailoring therapy to the degree of risk are most likely to promote optimal outcomes. (Reviewer-Craig M. Oliner, MD).

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**Keywords:** Acute Coronary Syndromes, Revascularization

**Print Tag:** Refer to original journal article
Early Transfer Best for High-Risk STEMI Patients Receiving Fibrinolysis or Early PCI

Routine Early Angioplasty After Fibrinolysis for Acute Myocardial Infarction.
Cantor WJ, Fitchett D, et al:


Transfer high-risk STEMI patients receiving fibrinolysis or early PCI within 6 hours.

**Background:** Primary percutaneous coronary intervention (PCI) is the preferred treatment for ST-segment MI (STEMI) when performed within 90 minutes of arrival to a hospital. Unfortunately, primary PCI is performed in <25% of U.S. hospitals, and transfer times preclude PCI within the ideal window of opportunity in most communities. In patients admitted to institutions without PCI capabilities, fibrinolysis is the treatment of choice. Most patients undergo cardiac catheterization and PCI following fibrinolysis. No adequately powered study has been conducted to define the appropriate strategy for STEMI management and the optimal timing of catheterization and PCI.

**Design/Objective:** Large, randomized trial comparing early transfer for catheterization and PCI with standard, later transfer for catheterization and PCI.

**Participants/Methods:** 1059 high-risk patients (systolic blood pressure <100 mm Hg, heart rate >100 bpm, Killip class II or III, ST-segment depression ≥2 mm in anterior leads, or ST-segment elevation in right-sided leads) with acute STEMI treated with fibrinolysis were included. Patients were randomized to either standard treatment or immediate transfer to a PCI center within 6 hours after fibrinolysis for cardiac catheterization and PCI.

**Results:** Patients assigned to standard treatment underwent catheterization 32.5 hours after fibrinolysis, and the routine, early PCI patients underwent catheterization 2.8 hours after fibrinolysis. The primary end point of death, reinfarction, recurrent ischemia, new or worsening congestive heart failure, or cardiogenic shock within 30 days occurred in 11.0% of patients in the early, routine PCI group and 17.2% of patients in the standard-therapy group (relative risk with early PCI, 0.64; \( P =0.004 \)). Urgent catheterization was necessary in 34.9% of patients in the standard therapy group. There were lower rates of recurrent ischemia (0.2% vs 2.1%), new or worsening heart failure (3.0% vs 5.6%), and reinfarction (3.4% vs 5.7%) in the routine, early PCI patients. No difference was found in death or major/severe bleeding between groups.

**Conclusions:** Among high-risk STEMI patients receiving fibrinolysis, transfer for early PCI within 6 hours was associated with fewer ischemic complications than standard therapy.

**Reviewer's Comments:** Primary PCI is the treatment of choice for acute STEMI when available within 90 minutes of arrival at the hospital. Unfortunately, this procedure is available in only 25% of U.S. hospitals. Therefore, fibrinolysis is used for many STEMI patients. Facilitated PCI with fibrinolytic therapy or a combination of fibrinolytic therapy and aggressive antiplatelet therapy is of no benefit. However, cardiac catheterization and PCI performed at a delayed time following fibrinolysis has been effective. The ideal time for the procedure has not been previously defined. With the current study by Cantor and colleagues, we now have confirmatory data to support previous smaller studies that routine, early cardiac catheterization and PCI is the most advantageous approach. (Reviewer-D. Lynn Morris, MD).

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Keywords: PCI, Fibrinolysis, MI

Print Tag: Refer to original journal article
Depression and Anxiety Make Angina Worse

Psychosocial Modulators of Angina Response to Myocardial Ischemia.

Arnold SV, Spertus JA, et al:

Circulation 2009; 120 (July 14): 126-133

Psychosocial factors play an important role in angina frequency in patients with documented ischemia.

Background/Objective: Angina is a common symptom of coronary artery disease that does not correlate exceptionally well with the degree of coronary artery disease. While there have been data suggesting that psychosocial factors have an impact on the degree of symptoms in patients with normal coronary arteries, there are few data on the impact of psychosocial factors on angina symptoms in patients with known coronary artery disease.

Methods: 1030 patients with clinically indicated myocardial perfusion scans were screened. Ultimately, 191 patients were willing to participate, had interpretable perfusion imaging, and had inducible ischemia. Participants completed various validated questionnaires including the Seattle Angina Questionnaire and psychosocial questionnaires to assess anxiety, depression, neuroticism, alexithymia (the ability to express inner feelings), and somatosensory amplification. Multivariate analysis was performed.

Results: Angina was categorized as none, monthly, or weekly/daily. Of the 191 patients, 36% had no angina, 35% had monthly angina, and 30% had weekly/daily angina. The mean age of participants was 63 years, and nearly 90% were men. Patients with lower self-reported angina scores were less likely to experience exertional angina on stress testing, and all psychosocial variables were associated with angina frequency on univariate analysis. With multivariate analysis, previous revascularization (OR, 3.06; 95% CI, 1.49 to 6.31), greater anxiety scores (OR, 1.39 per 1.2 SD increase in score), and greater depression scores (OR, 1.51; 95% CI, 1.17 to 1.93) were associated with increased angina frequency. If psychosocial variables were used as dichotomous variables, those with at least moderate anxiety had a 4.7 increased risk of having increased angina. Those with depression had a 3.1-fold increased risk of frequent angina.

Conclusions: There is an association between psychosocial factors and frequency of angina, with patients having weekly/daily angina being 44% more likely to have significant anxiety and 64% more likely to have clinically significant depressive symptoms.

Reviewer's Comments: This study demonstrates the role of psychosocial factors in angina symptoms in patients with documentable ischemia, emphasizing the role of psychosocial factors and ischemia in addressing overall symptom burden in these patients. (Reviewer-Karen Stout, MD).

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Keywords: Myocardial Ischemia, Angina, Psychosocial Factors, Symptoms

Print Tag: Refer to original journal article
The prognosis of asymptomatic patients with ventricular preexcitation appears to be good.

**Background:** The long-term outcome of asymptomatic adults with ventricular preexcitation (Wolff-Parkinson-White [WPW]) syndrome is not well defined. Because sudden cardiac death can sometimes be the first clinical presentation, patients often undergo pharmacological or nonpharmacological treatment, perhaps unnecessarily.

**Objective:** To determine the outcomes and predictors of arrhythmia in asymptomatic adults with ventricular preexcitation.

**Participants/Methods:** Between July 1995 and December 2005, adults >18 years of age, with an incidental finding of WPW pattern on ECG were enrolled. Patients underwent electrophysiological study (EPS) in an attempt to induce atrioventricular reentrant tachycardia (AVRT) and atrial fibrillation (AF). Potentially life-threatening arrhythmias were defined as sustained preexcited AF with a rate ≥240 bpm. Cardiac arrest was defined as an arrhythmia requiring CPR or defibrillation. The primary end point was occurrence of a clinical arrhythmia.

**Results:** 293 patients were screened, chose to participate, and underwent EPS. The median age was 36 years (range, 28 to 48 years). Of these patients, 180 were found to have WPW on an incidentally obtained ECG, whereas 113 cases were found during physical exams prior to sports activities. During EPS, 16% had inducible AF or AVRT. During follow-up, 79 patients (27%) lost evidence of preexcitation, and 31 patients (11%) developed arrhythmic events during follow-up. Of this group, 22 had been inducible during EPS. AVRT was sustained in 14 patients. The remaining 17 patients (6%) had potentially life-threatening arrhythmias, and 14 of these had been inducible during EPS. Patients who developed arrhythmia were younger, had more rapidly conducting accessory pathways, and were more likely to have multiple accessory pathways. Predictors of arrhythmic events or potentially life-threatening arrhythmias had younger age, rapidly conducting accessory pathways, and inducibility of arrhythmias during EPS.

**Conclusions:** Adults with asymptomatic ventricular preexcitation overall appear to have a good prognosis. Potential risk factors for dangerous arrhythmias include a younger age at diagnosis, inducibility of arrhythmias during EPS, and rapidly conducting accessory pathways.

**Reviewer's Comments:** Physicians wrestle frequently with appropriate management of asymptomatic patients with WPW. Recent dramatic advances in safety and efficacy of radiofrequency ablation techniques have led to more frequent and earlier ablation of accessory pathways. This study suggests that a conservative approach of risk stratification may be viable. Further analysis (including effectiveness of exercise testing and complications, costs, and utilization of EPS and ablation) is likely warranted. (Reviewer-Sumeet K. Mainigi, MD).

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Keywords: Wolff-Parkinson-White Syndrome, preexcitation, SVT

Print Tag: Refer to original journal article
Octreotide vs Prochlorperazine for Migraine Headaches

Randomized Evaluation of Octreotide vs Prochlorperazine for ED Treatment of Migraine Headache.

Miller MA, Levsky ME, et al:


Octreotide is not particularly helpful for migraine headaches, but IV prochlorperazine remains an outstanding choice for the treatment of severe migraines.

**Background:** Severe migraine headaches are a common cause of emergency department (ED) visits. There is some evidence that IV somatostatin is as effective as ergotamine for the short-term treatment of cluster headaches, and interest has grown to see if there could be efficacy for the treatment of migraine headaches. Prochlorperazine (PC) has effectiveness as an IV treatment of vascular headaches and has the benefit of no abuse potential. Somatostatin analogs (octreotide [OC]) would also share with PC the lack of abuse potential and, if effective for migraines, could be preferable due to fewer side effects.

**Objective:** To evaluate the efficacy of IV OC compared to PC for the treatment of migraine headache in the ED.

**Design/Participants:** Double-blind, randomized, controlled trial of patients with migraine headache treated in an ED. A total of 44 patients were enrolled.

**Methods:** Patients were randomized to receive either 100 μg of OC (24 patients) or 10 mg of PC (20 patients) as an IV bolus over 2 minutes. Patients rated the efficacy of treatment using a visual analog scale prior to treatment and again 60 minutes after treatment. Patients were also asked if they were satisfied with treatment.

**Results:** OC was less effective at reducing pain ($P=0.03$) and producing clinical success, at only 57% versus 90% for prochlorperazine ($P<0.01$). Only 2 patients who received PC required rescue medications compared to 11 patients who received OC. Two patients who received PC and 6 patients who received OC had recurrence of headache in <48 hours. Patients who received PC had significantly more side effects than those who received OC.

**Conclusions:** PC is superior to OC for the treatment of migraine headache.

**Reviewer’s Comments:** You may be wondering why I chose a negative study of a drug (OC) that we usually would not consider for the treatment of migraine headache. I was impressed by the high response rate for PC, which was very similar to the response rate of 88% in the biggest prior PC study from 1986. IV PC is an excellent option for the treatment of severe migraine headaches. If you prescribe it, be prepared for the side effects of akathisia and sedation that can occur. (Reviewer-Douglas S. Paauw, MD).

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Keywords: Migraine Headache, Octreotide, Prochlorperazine, ED

Print Tag: Refer to original journal article
Background: Parents who refuse immunizations for their children frequently cite pain as a reason. It is known that some vaccines are more painful than others. What is not known is if the order of administration affects the cumulative pain experience.

Objective: To determine if the pain response after administration of the diphtheria, polio, and tetanus toxoids and acellular pertussis and Haemophilus influenzae type B vaccine (DPTaP-Hib) and the pneumococcal conjugate vaccine (PCV) differed based on order of administration.

Design: Randomized, double-blind study.

Participants: Infants aged 2 to 6 months were assessed who did not have a known acute febrile illness, chronic health problem, or allergy to either immunization. Use of systemic analgesic was not an exclusionary factor.

Methods: 120 participants were randomly chosen to receive either the DPTaP-Hib or PCV first followed by the other vaccine. Administrators, care givers, and patients were all blinded, and needles appeared identical. Participants were videotaped, and 2 investigators reviewed their reactions immediately before and after administration. Their pain reaction was scored using the Modified Behavioral Pain Scale. Parents also evaluated their children's pain using the visual analog scale. Investigators also noted the presence or absence of crying.

Results: Pain after the first injection was significantly less when the DPTaP-Hib was administered first. Similarly, the overall pain score after administration of both vaccines was significantly lower when the DPTaP-Hib was administered first. Finally, in all participants, pain increased after the second immunization was administered, regardless of which vaccine was given first.

Conclusions: Administration of the DPTaP-Hib vaccine first resulted in less pain after the first injection and less pain overall following administration of both vaccines compared to administering the PCV first.

Reviewer's Comments: Our understanding of pain and the perception of pain is rapidly growing. Researchers have learned that earlier painful stimuli appear to have a negative impact on future reactions to painful stimuli. Therefore, it is important to determine the least painful way to deliver preventive medicine both to increase the likelihood that parents will agree to immunizations and to minimize the negative impact on later painful experiences and perceptions. This was a very well-designed study, with a simple question and clean results that add to this growing body of knowledge. (Reviewer-Lisa Humphrey, MD).

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Keywords: Vaccine, Injection Pain, Response

Print Tag: Refer to original journal article
Vaccines Are Not Lone Cause of Autism Spectrum Disorders

Prenatal, Perinatal, and Neonatal Factors Associated With Autism Spectrum Disorders.
Bilder D, Pinborough-Zimmerman J, et al:

Pediatrics 2009; 123 (May): 1293-1300

A number of factors, both maternal and perinatal, seem to be associated with autism spectrum disorder and warrant further investigation.

Background: Autism is a complicated condition with a host of potential associations, both genetic and environmental. The existence of twin and sibling concordance suggests a familial disposition, but incomplete concordance also means that there are likely outside factors as well. Although a number of factors have been associated with autism, no one factor has been shown to have a positive association consistently. These differences may be due, in part, to differences in study methodology.

Objective: To examine risk factors for autism spectrum disorders using rigorous methodologies and broad ascertainment.

Participants/Methods: The study population was 8-year-old children born in 1994 and living at 1 of the 3 most populous counties in the state of Utah; these 3 counties house about two thirds of the total population of the state. As part of the Autism and Developmental Disabilities Monitoring Network, multiple source screening occurred at all public schools and all major health sites in the area. Trained abstractors went to each site and reviewed records to look for autism spectrum disorder triggers that could lead to further investigation. Records were requested on 4549 children; 532 had an autism spectrum disorder trigger and 196 met criteria for diagnosis. These children were matched to 100 controls each on gender and birth year. Multivariate logistic regression was performed to determine associations with prenatal, perinatal, and neonatal factors.

Results: A number of factors were found to be significantly associated with a greater risk of autism spectrum disorder. These included having a mother aged >35 years (OR, 1.7) and being a first-born child (OR, 1.8). Children who presented in a breech position were also at higher risk (OR, 2.1), as were those born by cesarean section (OR, 1.7); after controlling for breech position as a cause of cesarean section, the association with cesarean section disappeared. Neonatal factors were not found to be associated with an increased risk of developing autism spectrum disorder.

Conclusions: A number of factors, both maternal and perinatal, seem to be associated with autism spectrum disorder and warrant further investigation. (1) Prenatal factors such as advanced maternal age and first in birth order seem to be associated with a higher risk of autism spectrum disorder. (2) Perinatal risk factors such as breech presentation also have a higher risk of autism. (3) Neonatal risk factors were not found to be associated with a higher risk.

Reviewer's Comments: With so much time spent perseverating on the vaccine issue, it is nice to see a study looking for factors with scientific evidence behind them. More work is needed to determine causes of autism and what might be done to treat it. (Reviewer-Aaron E. Carroll, MD, MS).

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Keywords: Autism Spectrum Disorders, Risk Factors

Print Tag: Refer to original journal article
Objective: To assess the predictive power of specific molecular markers (bcl-2, p53, and microvessel density [MVD]) on prostate cancer mortality.

Participants/Methods: 1313 veterans with prostate cancer between 1991 and 1995 were identified. Clinical data were collected from medical records for 1172 men through 2006. Tissue from initial diagnosis was obtained and stained for specific molecular markers, and analysis was then performed to correlate markers with clinical outcomes.

Results: Follow-up was from 11 to 16 years, over which time 71.8% of men died, 21.5% of whom died from prostate cancer. In addition to classic predictors of death from prostate cancer, such as PSA level and Gleason score, the markers bcl-2, p53, and MVD were all shown to be significant in predicting prostate cancer death.

Conclusions: Increased presence of the molecular markers bcl-2, p53, and MVD at diagnosis is associated with an increased risk of long-term death from prostate cancer.

Reviewer's Comments: There have been many marker studies in prostate cancer, and the ones used in the current trial are not new or novel. What sets this article apart is the study design. Commonly, marker studies compile a small series of tissue specimens and stain for various markers to find something interesting, in what can be considered a "cross-sectional" study design, which gives no information about prognosis. Instead, these authors chose to do something more ambitious. They used a cohort design, looking at only a few interesting markers, and looked at prostate cancer from 15 years earlier, so the findings would have 15-year follow-up. In addition, they powered the study well, by including >1000 men. The "cohort" design refers to how they compared 2 sets of patients. For example, they determined which patients had low MVD versus high MVD at diagnosis, 15 years earlier. Then they "followed" those patients over time to see if there were more deaths in one group or the other. This is the best way to answer a question about prognosis. Specifically, they found that the risk of prostate cancer death was increased by presence of bcl-2 (a marker for cell death, or "apoptosis") by 61%; p53 (a marker of cell-cycle regulation), by 48%; and increased MVD (a marker of blood vessel formation), by up to 320%. The bottom line is that all markers were found to be significant. While there are criticisms and limitations to this trial due to its retrospective nature, it is still one of the most interesting marker studies in recent times. With this type of conclusive data, we can move forward in determining the practical, clinical utility of these markers, and they may someday show up in our offices. (Reviewer-Steven E. Canfield, MD).

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Keywords: Cancer, Molecular Markers, Death

Print Tag: Refer to original journal article
Should Phototherapy Be Used Universally for Jaundice in Newborns?

*Numbers Needed to Treat With Phototherapy According to American Academy of Pediatrics Guidelines.*

Newman TB, Kuzniewicz MW, et al:

*Pediatrics* 2009; 123 (May): 1352-1359

Although phototherapy appears to be effective, its actual effectiveness is highly variable across different groups.

**Background:** Although recommendations of the American Academy of Pediatrics (AAP) for treatment of hyperbilirubinemia are specific, they correctly state that they are based on "uncertain estimates and extrapolations." The studies that have been used to estimate the number needed to treat (NNT) with phototherapy had different cutoff values for beginning and ending treatment than that recommended by the AAP. The true NNT is unknown.

**Objective:** To determine the true efficacy of phototherapy for jaundice in infants and to calculate the NNT to prevent 1 exchange transfusion.

**Methods:** A cohort of children was gathered from medical records in the Northern California Kaiser Permanente Medical Care Program, which covers >3 million members. Eligible infants were those born alive between 1995 and 2004, weighing ≥2 kg, and born at ≥35 weeks’ gestation. All data were drawn from electronic databases of the health care system. AAP guidelines were used to determine who should receive phototherapy and for how long. Infants in this analysis were those who had a total serum bilirubin level within 3 mg/dL of the threshold for age and risk group. Infants were excluded if their bilirubin was already declining or if the direct bilirubin was >2 mg/dL. Phototherapy was identified by procedure code.

**Results:** Of 281,898 infants in the birth cohort, 22,547 were eligible for analysis. Of these, about 31% had a procedure code for phototherapy. Based on review, the procedure code for phototherapy was both sensitive and specific for actually having undergone phototherapy. Phototherapy began within 8 hours of a qualifying total serum bilirubin level in about 75% of cases, for a total of 5251 infants. Of these, only 1.6% ever exceeded the level where exchange transfusion would be recommended. For infants with a negative direct antiglobulin test, phototherapy was very effective, with an adjusted odds ratio of 0.16. For infants with a total serum bilirubin above the treatment threshold, the NNT to prevent 1 exchange transfusion was 222 for boys and 339 for girls. There was significant variation in the effectiveness across subgroups, with high effectiveness in infants aged <1 day and low effectiveness in infants aged >3 days.

**Conclusions:** Although phototherapy appears to be effective, its actual effectiveness is highly variable across different groups. (1) Phototherapy does prevent exchange transfusions according to AAP guidelines. (2) The actual effectiveness varies across groups but with some high NNTs. (3) Further research should investigate the cost-effectiveness of phototherapy in infants.

**Reviewer’s Comments:** Although it appears effective, it may be that tailored phototherapy for certain subgroups may be more cost-effective. This is an area that begs for a cost-effectiveness analysis. (Reviewer-Aaron E. Carroll, MD, MS).

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**Keywords:** Phototherapy, Hyperbilirubinemia, Jaundice

**Print Tag:** Refer to original journal article
Cognitive Decline With Age Is Not Inevitable

Predictors of Maintaining Cognitive Function in Older Adults: The Health ABC Study.

Yaffe K, Fiocco AJ, et al:
Neurology 2009; 72 (June 9): 2029-2035

Older people who exercise, have at least a high school education, have a 9th grade literacy level, are nonsmokers, and are more socially active are more likely to maintain their cognitive skills as they age.

Background: Most studies of cognition in the elderly have focused on predictors of decline. Very little is known about factors associated with maintaining cognitive abilities during the aging process.

Objective: To identify characteristics associated with maintaining normal cognition during aging.

Design: Prospective cohort study.

Participants/Methods: 2509 well-functioning elders who were enrolled in the Health ABC Study were followed prospectively. The cohort included black and white women and men between the ages of 70 and 79 years at the time of enrollment (1997). The Modified Mini-Mental State Examination (3MS) was administered at baseline and at years 3, 5, and 8. Each participant's cognitive status was classified as maintaining function (cognitive slope change, ≥0), having minor decline (slope, <0 and >1 SD below the mean), or having major decline (slope, ≤1 SD below the mean). Logistic regression analysis was used to identify psychosocial, health, and biological factors associated with maintaining versus having a decline in cognition.

Results: Cognitive function was maintained in 30% of patients, 53% had a minor decline, and 17% had a major decline. In the multivariate-adjusted model, characteristics that were predictive of maintaining cognitive function versus having minor cognitive decline were age (OR, 0.65; 95% CI, 0.55 to 0.77 per 5 years), white race (OR, 1.72; 95% CI, 1.30 to 2.28), attaining a high school or higher education level (OR, 2.75; 95% CI, 1.78 to 4.26), having a 9th grade or higher literacy level (OR, 4.85; 95% CI, 3.00 to 7.87), engaging in weekly moderate to vigorous exercise (OR, 1.31; 95% CI, 1.06 to 1.62), and not smoking at baseline (OR, 1.85; 95% CI, 1.14 to 2.97). There was a trend toward maintaining cognitive function with working or volunteering, living with someone, and not having the apolipoprotein e4 allele. Factors that significantly predicted major versus minor cognitive decline were older age, having less than a high school education, lower than a 9th grade literacy level, having less social support, and the presence of the apolipoprotein e4 allele. There was a trend toward major decline with higher BMI, diabetes, hypertension, and race.

Reviewer's Comments: Conclusions/Reviewer's Comments: Factors associated with maintaining cognitive function appear to differ from those associated with cognitive decline. Working/volunteering, exercise, and not smoking are more predictive of maintenance of cognitive abilities than of a decline. Education and literacy levels are strong predictors of both maintenance and decline. The results of this study are encouraging since strategies for modifying these risk factors could have widespread impact on maintaining quality of life with aging and reducing societal costs associated with cognitive decline in the elderly. The authors point out that the effects of literacy and education level, although statistically controlled for, may still explain the association between race and changes in cognitive function with age. Further studies are needed to better understand these associations and to develop preventive strategies. (Reviewer-Elaine Sachter, MD).

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Keywords: Cognitive Decline, Prevention

Print Tag: Refer to original journal article
Medical therapy is reasonable in most type 2 diabetics with stable coronary disease.

**Background/Objective:** Diabetics have a higher risk of death and major cardiovascular events than other individuals. Whether prompt revascularization can reduce this risk is unknown. It is also unclear if insulin sensitization therapy is more beneficial/less harmful than insulin provision.

**Participants/Methods:** 2368 patients were enrolled at 49 sites throughout the world and followed up for a mean of 5.3 years. Eligibility required both type 2 diabetes and severe atherosclerosis of at least 1 coronary artery by coronary angiography. All subjects had to be revascularization candidates, with the treating physician deciding whether CABG or PCI was most appropriate; those requiring immediate revascularization or with left main disease were excluded. After type of revascularization was elected, patients were randomized in a 2-by-2 factorial fashion to medical therapy versus revascularization and insulin sensitization (metformin, thiazolidinedione) versus insulin provision (insulin, sulfonylurea). Primary outcome was all-cause death; secondary outcome was death/MI/stroke.

**Results:** Survival at 5 years was similar in the revascularization and the medical therapy groups (88.3% vs 87.8%) and between the insulin-sensitization and insulin-provision groups (88.2% vs 87.9%). Rates for the secondary end point were also similar and were not significantly different among these groups. Those in whom CABG was predesignated had more extensive disease and, when randomized to revascularization, had less death/MI/stroke than with medical therapy alone (22.4% vs 30.5%; \(P = 0.01\)). In the PCI stratum, no such difference was seen. Severe hypoglycemia was more common with insulin provision than insulin sensitization (9.2% vs 5.9%; \(P = 0.003\)).

**Conclusions:** Prompt revascularization did not affect either end point in this group of type 2 diabetics, neither did the type of hypoglycemic therapy selected. In patients designated as candidates for CABG by the treating physician, revascularization was associated with a decrease in major cardiovascular events versus medical therapy alone. Insulin-sensitization therapy had benefits in overall glycemic control and some biometric parameters.

**Reviewer’s Comments:** This is a complex study, loaded with useful information, but it does have limitations. Recruitment targets were not met, and observed events were less than anticipated, thus limiting the power of the study. In addition, by 5 years, 42% of the medical therapy patients had crossed over to some kind of revascularization. Nevertheless, these data, in combination with the recent COURAGE study, strongly suggest that stable patients need not undergo immediate revascularization, regardless of whether they are diabetic. Furthermore, in line with the original BARI study, it seems likely that diabetic patients with extensive coronary disease do better with CABG than PCI. Finally, the jury is still out on the usefulness of insulin sensitizers, particularly thiazolidinediones, for the prevention of cardiovascular events. Some recent data suggest possible harm, but this study showed better glycemic control, fewer episodes of severe hypoglycemia, and improved HDL with insulin-sensitization therapy. (Reviewer-Gregg S. Pressman, MD).

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**Keywords:** Type 2 Diabetes, Coronary Disease, Revascularization, Insulin-Sensitization

**Print Tag:** Refer to original journal article
The number of preventable adverse events should be the primary outcome parameter associated with reduced resident work hours. The effectiveness of reduction in work hours in this regard is unknown.

**Objective:** To determine the approximate increase in labor costs associated with transfer of workload from residents to substitute providers in teaching hospitals.

**Design:** Hypothetical, probability model designed to estimate preventable adverse events, net costs, and cost-effectiveness associated with reduced resident hours.

**Methods:** 1206 hospitals with Accreditation Council for Graduate Medical Education (ACGME)-accredited programs were assessed. Investigators designed a 2-step study to estimate labor costs across hospitals and net costs and cost-effectiveness at major teaching hospitals. They developed a probability model that represented labor costs, mortality, and costs associated with adverse events that could be prevented in these hospitals. The model included variables of the current work week, duration and frequency of extended shifts, and time on inpatient rotations. The authors then evaluated the effect of 4 recommendations by the Institute of Medicine (IOM) and their transfer of current workload to substitute providers. These recommendations include improved adherence to an 80-hour work week by transferring workload to midlevel providers and attending physicians. The IOM also recommended protected naps during extended shifts, with 16-hour limits for shifts without naps and reduced workload. For purposes of this study, investigators assumed that individual substitutes would perform excess work transferred from multiple residents. The model also accounted for additional resident slots as recommended by the ACGME and cost savings that may be incurred by preventable adverse events.

**Results:** Based on this model calculation, annual labor costs for implementing the IOM recommendation is estimated to be $1.6 billion across all ACGME-accredited programs in the United States. The range of sensitivity for this analysis was from $1.1 to $2.5 billion. When the society cost was analyzed to prevent 1 death by implementing these recommendations, the cost was $3.4 million to $0. Assuming a range of 10% decrease to 10% increase in preventable adverse events, net costs per admission for implementation of IOM recommendations would range from $99 to $183 for major teaching hospitals and $17 to $266 for society as a whole.

**Conclusions:** The net cost for implementing the 4 IOM recommendations for resident work hours would result in a high cost to teaching hospitals. Overall, recommendations would be costly, their effectiveness is unknown, and, in the best-case scenario, they can prevent patient harm at reduced or no cost to society.

**Reviewer's Comments:** There are valid studies that show objective impairment secondary to extended work hours. However, the issue of reducing resident work hours is not that simple. The concentration and intensity of experience gained must be carefully balanced against impairments to learning and patient care associated with prolonged hours. This study clearly states that reducing resident work hours results in significant increases in costs on both education and patient care. (Reviewer-John C. Jennings, MD).

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Keywords: Resident Physicians, Reduced Work Hours, Workloads

Print Tag: Refer to original journal article