Watch Out for *H pylori*-Negative Ulcers

*High Incidence of Mortality and Recurrent Bleeding in Patients With Helicobacter pylori*-Negative Idiopathic Bleeding Ulcers.*

Wong GL, Wong VW, et al:

Gastroenterology 2009; 137 (August): 525-531

Recurrent bleeding is much more common when *Helicobacter pylori* is not present in a peptic ulcer.

**Background:** Risk of recurrent bleeding from *Helicobacter pylori*-negative ulcers is greater than for *H pylori* ulcers, but to what degree is unknown.

**Objective:** To determine the risk of rebleeding for peptic ulcers with and without associated *H pylori* infection.

**Design:** Prospective cohort study in 1 institution over 7 years.

**Participants:** 120 patients had *H pylori*-negative peptic ulcer bleeding and 213 had bleeding associated with *H pylori* infection.

**Methods:** *H pylori*-negative patients had to have no exposure to NSAIDs, aspirin, or other medications within 4 weeks of the bleeding episode, negative results for *H pylori* on biopsies and the urease test taken during index endoscopy for bleeding, and no other evident cause of ulceration. Both groups were treated appropriately. Follow-up endoscopy was done to document healing. No long-term gastroprotective therapy was used. Primary end point was recurrent bleeding. Mortality was a secondary end point.

**Interventions:** All patients had endoscopy for recurrent bleeding. Biopsies and urease test were also repeated during recurrent bleeding episodes. Drugs associated with gastric injury were prohibited during the study period.

**Results:** *H pylori*-negative ulcer patients were older, had more gastric ulcers, and had more recurrent bleeding during the index hospitalization. Median follow-up was 30 months (range, 1 to 89 months) in *H pylori*-negative patients and 79 months (range, 1 to 89 months) in *H pylori*-positive patients. The 7-year cumulative rebleeding rate for *H pylori*-negative patients was 42% compared to 11% for *H pylori*-positive patients. When NSAID use and recurrent *H pylori* infection were excluded, the recurrent bleeding rate was 25% versus 3%. Mortality was higher in *H pylori*-negative patients and only correlated with American Society of Anesthesiology grade ≥3. *H pylori*-negative status was an independent predictor of recurrent bleeding and mortality.

**Conclusions:** *H pylori*-negative bleeding ulcers are associated with an increased risk of rebleeding and mortality compared to *H pylori*-positive bleeding ulcers.

**Reviewer's Comments:** Very interesting long-term study of patients with peptic ulcers that bled. Groups were followed based on presence of *H pylori* infection at the time their ulcer bled. The recurrent bleeding rate was significantly higher among patients who did not have *H pylori* infection. The rebleeding rate was extremely low for *H pylori*-positive patients after *H pylori* eradication unless recurrent infection occurred or NSAID use was documented. The shorter follow-up among *H pylori*-negative is explained by the higher mortality rate. Age could be a factor for recurrent bleeding, although this did not appear to be true based on statistical analysis. The authors make a strong case that *H pylori*-negative ulcers are different. They suggest that long-term gastroprotective treatment should be considered. (Reviewer-John A. Weigelt, MD).

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Keywords: Peptic Ulcer, Bleeding, Mortality, *Helicobacter pylori*

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Consider Rebound Effect When Stopping PPIs

Proton Pump Inhibitor Therapy Induces Acid-Related Symptoms in Healthy Volunteers After Withdrawal of Therapy.

Reimer C, Søndergaard B, et al:

Gastroenterology 2009; 137 (July): 80-87

Use of proton pump inhibitors (PPIs) for >8 weeks can result in acid hypersecretion and worsening of symptoms when PPIs are stopped.

**Background:** Proton pump inhibitors (PPIs) suppress acid secretion and may be responsible for a proliferation or hyperactivity of gastric G cells. Discontinuation of PPIs may result in an increase in acid-related symptoms, which could then be mistaken for recurrence of the disease, resulting in restarting of the PPIs.

**Objective:** To determine the effect of PPI cessation on healthy individuals (for whom disease recurrence would not be a confounding issue).

**Design:** Double-blind, randomized controlled trial.

**Participants:** Healthy subjects without any significant history of dyspepsia or reflux.

**Methods:** Volunteers were randomized (using a scheme generated by the pharmaceutical company) into 1 of 2 arms. PPI recipients were given 40 mg esomeprazole for 8 weeks and then a matching placebo for 4 weeks. Controls were given placebos for the entire 12-week period. A validated 15-item Gastrointestinal Symptom Rating Scale (GSRS) was completed weekly. The primary outcome was the combined score from the 3 items that assessed dyspepsia, heartburn, and reflux. Other outcomes included the total GSRS score, number of patients in each group who developed a score of ≥2 on at least 1 of 3 items in the primary outcome in weeks 9 to 12, the 36-item Short-Form Health Survey (SF-36) score, use of rescue antacid tablets, and serum gastrin and chromogranin A levels. (The latter level reflects gastric G-cell activity.) No a priori sample size calculation seems to have been done.

**Results:** A total of 120 patients (60 in each group) were randomized, but 1 PPI recipient dropped out. The primary outcome score began to be higher in PPI recipients in the 9th week, and differences were statistically significant in weeks 10 to 12. More patients in the PPI group developed at least 1 score ≥2. PPI recipients took more antacid tablets in weeks 9 to 12. Serum gastrin and chromogranin A levels were higher at weeks 8 and 12. No significant differences were seen between groups with respect to total GSRS or SF-36 scores.

**Conclusions:** Stopping PPIs after using them for 8 weeks resulted in reflux/dyspeptic symptoms in healthy individuals, suggesting that the rebound acid hypersecretion of PPI usage is a clinically consequential event.

**Reviewer’s Comments:** PPIs can increase serum gastrin levels, a phenomenon that should be remembered whenever serum gastrin levels are being ordered to assess patients for Zollinger-Ellison syndrome. More importantly, we need to remember this acid rebound effect when we decide to discontinue PPI therapy in particular patients. They should be (1) advised to expect a short-lived period (probably a few weeks) when acid-related symptoms may get worse and (2) encouraged to get through that period without restarting PPIs.

(Reviewer-Ronald L. Koretz, MD).

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Keywords: Acid Secretion, Gastrin, Proton Pump Inhibitors

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Using data from the National Cancer Institute’s population-based SEER database, the authors estimated that >1 million men have been diagnosed and treated for prostate cancer over the past 20 years, indicating overdiagnosis.

**Background:** Screening for prostate cancer with a combination of prostate-specific antigen (PSA) testing and digital rectal exam (DRE) remains controversial, even with the recent publication of 2 randomized controlled trials of screening for cancer of the prostate (CaP). These and previous studies have raised concerns about overdiagnosis and overtreatment, or the idea that some or many CaP diagnoses may not have become clinically overt and therefore need not to have been aggressively treated.

**Objective:** To compare the age-specific incidence of CaP during the PSA before and after the widespread adoption of PSA-based screening.

**Methods:** The authors started with the assumption that the age-specific incidence of clinically relevant CaP remained stable throughout the study period (1985 to 2005). They then proposed that any sustained difference in the observed age-specific incidence of CaP represented over- or underdiagnosis. They used population-based data from the National Cancer Institute’s SEER (Surveillance, Epidemiology, and End Results) program, comparing the age-specific CaP incidence in 1986 (before PSA was introduced) to CaP incidence over the subsequent 19 years (1987 to 2005). Incidence rates were condensed into 5 age groups: 20 to 49 years, 50 to 59 years, 60 to 69 years, 70 to 79 years, and ≥80 years. Initial treatment data were also obtained from the SEER database. The incidence was transformed into U.S. population estimates based on age-specific U.S. Census data.

**Results:** The CaP incidence rose by 26% between 1986 and 2005. Age-specific incidence rates increased by 90% (RR, 1.91; 95% CI, 1.8 to 2.0) among men aged 60 to 69 years, more than tripled among men aged 50 to 59 years (RR, 3.64; 95% CI, 3.3 to 4.0), and increased >7-fold among men aged <50 years (RR, 7.23; 95% CI, 6.4 to 8.2). Using age-specific U.S. Census data, the authors estimated that an excess of 1,305,600 men were diagnosed and 1,004,800 were treated for CaP since 1986.

**Conclusions:** An excess of >1 million men in the U.S. have been diagnosed and treated for CaP during the past 20 years. This increased incidence was most dramatic among men aged <60 years and seems to indicate overdiagnosis.

**Reviewer’s Comments:** The authors posited that the observed increase in CaP incidence rates was due to overdiagnosis—that is, cancers that would not have become clinically apparent. The recently published European PSA screening study found that about 50 men would have to be diagnosed and treated to prevent 1 cancer death; the recently published U.S. randomized trial found no benefit to PSA screening, so the actual estimate of overdiagnosis (and overtreatment) probably ranges between 50 and infinity. Of note, treatment consequences and adverse events are immediate and long lasting, while potential benefit is deferred in time. (Reviewer-Paul R. Sutton, PhD, MD).
Among community-dwelling elders, participation in cognitively stimulating leisure activities was associated with an overall 50% decreased risk for dementia in this study.

**Background:** Prospective studies have found that participation in leisure activities is associated with maintaining cognitive function and a reduced risk of dementia in the elderly. It would be beneficial to know if specific types of leisure activities contribute to cognitive reserve and prevention of dementia. Cognitively stimulating activities may impart more protection than other types of activities.

**Objective:** To study the association between participation in various types of leisure activities and the risk of dementia.

**Design:** Observational cohort study.

**Participants/Methods:** Participants were part of a French cohort of community-dwelling elders aged ≥65 years. Information on types and frequency of leisure activities, health history, and socio-demographic variables were obtained from questionnaires. Activities were categorized as follows: cognitively stimulating (playing cards, working on crossword puzzles, attending organizational activities and movies/theater, engaging in an artistic activity), passive (listening to radio/music, watching TV, knitting/sewing), physical (gardening, walking, household jobs), or social (meeting with friends/relatives). Participants were screened for dementia at baseline and at 2 and 4 years of follow-up. Dementia was classified as Alzheimer disease (AD), mixed/vascular dementia, or other. Hazard ratios were calculated for incident dementia in relation to types of leisure activities. Analyses were adjusted for potential confounding variables including age, health status (including depression and vascular risk factors), educational level, and occupational attainment.

**Results:** Among 5698 participants who were free of dementia at baseline, 161 new cases of dementia were diagnosed (76 at 2 years and 85 at 4 years). Of these, 105 were diagnosed with Alzheimer disease, 38 with mixed/vascular, and 18 with other dementias. Cognitively stimulating leisure activities were independently associated with a reduction in the overall risk of dementia (HR, 0.49; 95% CI, 0.31 to 0.79) and Alzheimer disease (HR, 0.39; 95% CI, 0.21 to 0.71). There were no associations between other forms of leisure activities and the overall risk of dementia.

**Conclusions:** Cognitively stimulating leisure activities may delay onset of dementia in community-dwelling elders.

**Reviewer’s Comments:** In this study, participation in cognitively stimulating leisure activities at least twice a week was associated with an overall 50% decreased risk of dementia and a 60% decreased risk of Alzheimer type dementia. The lack of a significant association with mixed/vascular dementia may be due to the small number of cases. This finding was independent of educational level, occupational attainment, cognitive functioning at baseline, and participation in other leisure activities. I will continue to encourage patients to remain physically, socially, and cognitively active as they age and will emphasize that activities that are cognitively stimulating appear to have a uniquely protective effect against dementia. (Reviewer-Elaine F. Sachter, MD).

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Keywords: Dementia, Prevention, Leisure Activities

Print Tag: Refer to original journal article
Psyllium Better Than Bran for IBS Symptoms

Soluble or Insoluble Fibre in Irritable Bowel Syndrome in Primary Care? Randomised Placebo Controlled Trial.

Bijkerk CJ, de Wit NJ, et al:

BMJ 2009; 339 (August 27): b3154

Psyllium appears to be more effective than bran in reducing symptoms in patients with irritable bowel syndrome.

Background: Irritable bowel syndrome (IBS) is common, with a prevalence of approximately 10%, and treatment is challenging. Most primary care physicians recommend increasing fiber intake, often in the form of insoluble fiber (bran). The degree to which fiber (both soluble and insoluble) is effective for IBS symptoms is unclear.

Objective: To determine the effectiveness of soluble and insoluble fiber on symptoms and quality of life in patients with IBS.

Design: Randomized placebo-controlled trial, blinded to patients and study authors.

Participants: Patients in the Netherlands aged 18 to 65 years with a prior diagnosis of IBS (within 2 years) or with a new diagnosis (during the study) were invited to participate. Inclusion criteria were symptoms within the last 4 weeks with either "definite" IBS according to Rome II criteria or "probable" IBS as diagnosed by their primary care physician. Exclusion criteria were other organic bowel disease, fiber treatment within the last 4 weeks, or specialist treatment for IBS in the prior 2 years.

Methods: Patients were randomized to 10 g psyllium (soluble), 10 g bran (insoluble), or 10 g rice flour (placebo) for 12 weeks. Primary outcome was response to "did you have adequate relief of IBS symptoms in the past week?"; secondary outcomes were symptom severity, abdominal pain, and quality of life, each assessed by questionnaire after 1, 2, and 3 months of treatment.

Results: 275 patients were randomized (94% white; 78% female; mean age, 34.4 years). During the trial, approximately 40% of patients dropped out of the study (similar in each arm), mostly for "feeling worse" on treatment. In the intention-to-treat analysis, response (>2 weeks of adequate symptom relief per month) was significantly higher for psyllium than for placebo at 1 month (57% vs 35%; relative risk [RR], 1.6; number needed to treat [NNT], 4.0) and at 2 months (59% vs 41%; RR, 1.44; NNT, 5.9) but not at 3 months. Psyllium appeared most effective in patients whose symptoms fit Rome II criteria. In the third month, bran appeared more effective than placebo (57% vs 32%; RR, 1.7). Severity of symptoms was also improved at month 3 in the psyllium arm. Adverse events were similar across groups (mostly constipation and/or diarrhea).

Conclusions: Psyllium (rather than bran) appears to be an effective treatment approach in patients with IBS.

Reviewer's Comments: This nice trial shows that psyllium is probably superior to bran for control of IBS symptoms. Patients who self-select into this kind of study may be different (more intense abdominal pain, more consultations, etc) than all-comers with IBS, and once the study was ongoing, many folks dropped out. Thus, the results aren't completely generalizable and may be overconfident. Furthermore, this is a short study of only 3 months, and researchers were unable to show symptom improvement beyond 1 and 2 months. However, treatment with psyllium is safe, fairly inexpensive, and seems worth a try in our IBS patients. (Reviewer-Molly Blackley Jackson, MD).

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Keywords: Irritable Bowel Syndrome, Fiber, Bran

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Chronic anticoagulation with warfarin is associated with a net clinical benefit, balancing risk for ischemic stroke and intracranial hemorrhage. Patients at higher risk of stroke benefit most.

**Background:** The decision to chronically anticoagulate patients with atrial fibrillation (Afib) represents a balance of estimates of the relative benefit and harm in terms of stroke risk, as well as patient preference. Anticoagulation reduces the risk of stroke, but it increases hemorrhagic risks. Accurate estimates of the relative benefit and potential harm are difficult in clinical practice.

**Objective:** To measure the net clinical benefit of anticoagulation with warfarin in patients with chronic Afib.

**Methods:** The authors used the large ATRIA cohort (AnTicoagulation and Risk Factors In Atrial Fibrillation) to measure risks and benefits of anticoagulation. The ATRIA cohort is comprised of 13,559 patients from the Kaiser Permanente health care system of Northern California who have been followed since 1998. They recorded stroke risk factors (age, sex, heart failure, coronary artery disease, hypertension, and previous history of stroke) and warfarin exposure. The primary outcome was "net clinical benefit" combined with the decreased risk of stroke in patients taking warfarin minus 1.5 times the increased risk of intracranial hemorrhage (intracranial hemorrhage was multiplied by 1.5 because of frequently devastating neurological consequences of hemorrhage). They performed sensitivity analyses using different multipliers to explore the impact of intracranial hemorrhage on net clinical benefit.

**Results:** Average age of the cohort was 73 years, and approximately half were receiving warfarin at entry into the cohort. Patients were followed up for a median of 6 years. The average annual ischemic stroke risk was 2.1% (95% CI, 1.96% to 2.28%). On average, the net clinical benefit of warfarin was 0.68 adverse events prevented per 100 patient-years (95% CI, 0.34 to 0.87). The benefit associated with warfarin use increased as absolute stroke risk (estimated by the CHADS2 score) increased; the risk of intracranial hemorrhage remained relatively constant. Thus, the net clinical benefit increased as a function of age and other stroke risk factors. The net clinical benefit was highest among patients with a prior history of stroke, 2.48 per 100 patient-years (95% CI, 0.75 to 4.22). Varying the multiplier for intracranial hemorrhage between 1.0 and 2.0 did not significantly affect the results.

**Conclusions:** Chronic anticoagulation with warfarin is associated with a net clinical benefit, balancing risk for ischemic stroke and intracranial hemorrhage. Patients at higher risk of stroke benefit most.

**Reviewer’s Comments:** This is a valuable addition to the literature on chronic anticoagulation for Afib for 2 reasons: (1) this is a modern cohort with a lower average risk of stroke than seen in earlier studies, which would tend to bias against anticoagulation; and (2) it supports earlier studies suggesting that patients at highest risk for stroke derive the greatest benefit from anticoagulation. In general, patients with a CHADS2 score of ≥2 clearly benefit from anticoagulation. (Reviewer-Paul R. Sutton, PhD, MD).

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Keywords: Atrial Fibrillation, Anticoagulation, Warfarin, Risk-Benefit Analysis

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Background: In patients with atrial fibrillation (Afib), there has been interest in finding a treatment with the efficacy in stroke prevention of warfarin but with lower rates of bleeding and greater ease of administration. The thrombin inhibitor ximelagatran had shown promise but was rejected by the FDA due to concerns over liver toxicity.

Objective: To determine if dabigatran, an oral thrombin inhibitor, might be an effective alternative to warfarin in the management of Afib.

Design: Multicenter, randomized trial.

Participants: Patients were recruited from 951 centers from 44 countries. To be eligible, Afib had to have been documented in the previous 6 months, and at least 1 other risk factor had to be present (previous transient ischemic attack/stroke, ejection fraction <40%, class II or higher heart failure, age of at least 75 years, or age 65 to 74 years with hypertension, diabetes, or coronary artery disease).

Methods: Patients were randomized to warfarin or 1 of 2 doses of dabigatran (110 mg twice daily or 150 mg twice daily). The 2 doses of dabigatran were blinded, but warfarin use was unblinded. Patients were followed up regularly, including frequent liver function testing, for 2 years. The primary outcome was the rate of stroke or systemic embolism. All outcomes were adjudicated by independent investigators.

Results: 18,113 patients were enrolled, with an average age of 71 years and a mean CHADS2 score of 2.1. Roughly 50% of patients were being treated with warfarin at study onset. The rate of stroke or systemic embolism was lowest with dabigatran 150 mg (compared to both warfarin and the lower dose of dabigatran). The incidence of major bleeding was lowest in the low-dose dabigatran group (with similar rates in the higher dose and warfarin groups). In the higher-dose dabigatran group, gastrointestinal bleeding and myocardial infarction occurred more frequently than in the warfarin group. Hemorrhagic stroke was lower in both dabigatran groups compared to the warfarin group. No significant differences were seen in liver function abnormalities.

Conclusions: In patients with Afib, lower-dose dabigatran had a comparable rate of systemic embolism or stroke to that of warfarin but had a lower bleeding rate. With a higher dose of dabigatran, rates of embolism/stroke were lower than with warfarin, but overall bleeding rates were similar.

Reviewer's Comments: Thrombin inhibitors have shown promise as an alternative to warfarin in patients with Afib, with fixed dosing and no anticoagulant monitoring needed. Now, in this company-sponsored multicenter trial, dabigatran appears to be at least as effective as warfarin in reducing stroke with similar or less bleeding. Especially notable was the reduction in hemorrhagic stroke. The FDA will be reviewing this drug for approval in 2010. If approved, the next hurdle will be cost comparisons to warfarin. (Reviewer-Mark E. Pasanen, MD).
For maintenance of sinus rhythm in patients with atrial fibrillation, dronedarone is better tolerated than amiodarone but is less effective.

**Background:** Atrial fibrillation (Afib) is a common arrhythmia, and patients frequently require rhythm-controlling therapy rather than rate control alone. The best medication for controlling Afib is amiodarone; however, it is limited by toxicities largely related to the iodine component of the drug. Dronedarone is a new, non-iodinated antiarrhythmic that is similar to amiodarone and, theoretically, has fewer side effects than amiodarone. There have been several trials of dronedarone versus placebo, but few direct comparisons of amiodarone and dronedarone.

**Objective:** To perform a meta-analysis to compare the efficacy of dronedarone to that of amiodarone.

**Design:** Meta-analysis of trials comparing amiodarone or dronedarone to placebo as well as to each other.

**Methods:** Standard meta-analysis methods were used. Inclusion criteria included randomized trials of patients with Afib using 1 of these 2 medications, with follow-up of >6 months and end points including recurrent Afib and/or all-cause mortality. Exclusion criteria were studies of patients aged <18 years with postoperative Afib or studies with patients who underwent cardioversion or ablation.

**Results:** 88 amiodarone and 10 dronedarone studies were identified, and 83 amiodarone and 5 dronedarone studies were excluded. There were 4 randomized placebo-controlled trials (RCT) of dronedarone, with 5967 patients total, and 4 RCTs of amiodarone with 669 patients. Mean age across the 8 RCTs was 65 years, and 70% of patients were men. Ejection fraction was >50% in all trials, and patients were followed up for 6 to 22 months. The indirect meta-analysis estimated that amiodarone was better at preventing recurrent Afib compared with dronedarone (odds ratio [OR], 0.16; 95% CI, 0.06 to 0.42), which is the equivalent of 360 fewer events per 1000 patients treated. There was a mortality trend (not statistically significant) toward increased mortality with amiodarone (OR, 2.2; 95% CI, 0.61 to 7.99), with an increased likelihood of study drug discontinuation with amiodarone (OR, 6.65; 95% CI, 1.13 to 39.3).

**Conclusions:** Amiodarone is better at controlling Afib than is dronedarone, but amiodarone is associated with more side effects that result in discontinuation of medication. There are not enough data to suggest a mortality benefit of dronedarone.

**Reviewer's Comments:** Dronedarone is receiving publicity as the safer alternative to amiodarone. This meta-analysis confirms findings of 1 RCT, stating that dronedarone is less effective than amiodarone but is less toxic as well. Clearly, more data over a longer period are needed to determine whether the balance of effects conveys a significant benefit to dronedarone over amiodarone. (Reviewer-Karen Stout, MD).

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Keywords: Atrial Fibrillation, Medical Management, Dronedarone, Amiodarone

Print Tag: Refer to original journal article
Routine extending dual antiplatelet therapy to more than 12 months after percutaneous coronary intervention cannot be recommended, based on current available data.

**Background:** Current guidelines recommend dual antiplatelet therapy (DAT) with aspirin and a thienopyridine, usually clopidogrel, for at least 12 months after percutaneous coronary intervention (PCI) with a drug-eluting stent (DES). It is not clear whether patients who survive event-free after 12 months of DAT would benefit from longer treatment.

**Objective:** To assess the impact on clinical outcomes of prolonging DAT beyond 12 months.

**Design:** Single-center observational study.

**Participants:** 1859 patients who underwent PCI with either a bare-metal stent (BMS) or DES for stable or unstable disease and survived 365 days without myocardial infarction (MI) or target-vessel revascularization (TVR) were included. Patients with prior PCI, cardiogenic shock, bypass- graft PCI, or without data regarding duration of clopidogrel therapy were excluded.

**Methods:** After stents were placed, patients were advised to take 81 to 325 mg of aspirin daily indefinitely. Duration of treatment with clopidogrel was at the referring cardiologists' discretion. The primary end point was all-cause death or MI.

**Results:** Outcomes for those who received DAT for >12 months (n=918, 49%) were compared with outcomes of those who received DAT for ≤12 months (n=941, 51%). Subset analysis was performed on those receiving DES (n=1024), those receiving BMS (n=835), those with diabetes (n=486), patients presenting with MI (n=713), and patients with high-risk type-C lesions (n=717). DAT >12 months independently correlated with higher body weight, history of diabetes, history of hypertension, DES placement, and use of intra-aortic balloon pump during PCI. At a median follow-up of 3.5 years, death or MI occurred in 86 patients (9.4%) with extended DAT and in 97 patients (10.3%) who had DAT ≤12 months. Overall, the duration of DAT did not affect the likelihood of death or MI. The likelihood of definite or probable stent thrombosis also did not significantly differ between groups. Neither DES nor BMS benefited from extended DAT. The other predefined high-risk subsets also did not benefit from DAT >12 months.

**Conclusions:** After PCI with a DES, no advantage is achieved by extending dual antiplatelet therapy beyond 12 months.

**Reviewer's Comments:** This observational study demonstrated a lack of clinical benefit to extended DAT regardless of the type of stent used and despite the presence of risk factors for future thrombotic events. Other observational studies have yielded conflicting results, but data from the TAXUS II, IV, and V studies also demonstrated a lack of clinical benefit to DAT longer than 12 months. Routinely extending DAT to >12 months after PCI with stent cannot be recommended based on current available data. Consideration can be given to select patients only after carefully balancing potential benefits versus risks. The authors note that a randomized trial would best settle this question. (Reviewer-Parul B. Patel, MD).

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**Keywords:** Percutaneous Coronary Intervention, Dual Antiplatelet Therapy, Coronary Stent

**Print Tag:** Refer to original journal article
Approximately 70% of adolescents remain in remission for depression after active treatment is diminished in intensity or discontinued.

**Background/Objective:** The Treatment for Adolescents with Depression Study (TADS) posed a series of pressing treatment questions that began in 1999 and has generated many research papers, with wide-ranging findings. The main finding was that cognitive behavioral therapy (CBT) alone was less effective than combined treatment or fluoxetine alone and was not significantly more effective than placebo at week 12. CBT caught up with fluoxetine at week 18, and combined treatment reached maximal medical benefit at that point, several months earlier than fluoxetine or CBT. All treatments converged on an approximately 80% response rate by week 36. This paper reports on the 1-year naturalistic follow-up, termed stage IV, in which the TADS treatments were stopped and treatment was available in the community.

**Methods:** Immediately before the week-36 visit, which constituted the end of active treatment, each subject's clinical status was assigned an end-of-treatment score on the severity measure of the Clinical Global Impressions (CGI) scale. This score was used, in conjunction with a history of relapse, to recommend ongoing community-provided treatment. Participants were then reassessed at 6 months and 1 year into the community-provided treatment with the Children’s Depression Rating Scale-Revised, the CGI, and the Reynolds Adolescent Depression Scale.

**Results:** 234 of the original 430 subjects completed the 36-week assessment for entry into this part of the trial. Of these, 215 participated in at least 1 of the stage IV assessments. The adjustment rates of response at the 12-month follow-up assessment found no significant difference among the 3 initial treatment groups (combined treatment, fluoxetine alone, or CBT alone). There was also no statistically significant difference among the 3 treatment groups in terms of the loss of remission status at 1 year, averaging around 30% for each group relapsing.

**Conclusions:** Approximately 70% of continuation subjects from the initial TADS remain in remission, with no differences identified based on original treatment assignment and with relatively few subjects receiving ongoing care.

**Reviewer's Comments:** The major findings of the TADS team are as follows: combined treatment meaningfully accelerates recovery from depression relative to CBT and fluoxetine alone, but longer-term results may be similar; longer-term treatment decreases the chances of relapse or recurrence when treatment is discontinued; and adding CBT to fluoxetine minimizes persistent suicidal ideation and treatment-emergent suicidal events associated with medication monotherapy. (Reviewer-John G. Koutras, MD).

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Keywords: Adolescent Depression, Selective Serotonin Reuptake Inhibitors, Cognitive Behavioral Therapy

Print Tag: Refer to original journal article
Breastfeeding in infancy, for at least 1 month, is inversely correlated with adult body mass index and is positively associated with HDL cholesterol levels.

**Objective:** To determine if a relationship exists between breast-feeding in infancy and subsequent adult cardiovascular disease risk factors.

**Design/Methods:** Retrospective study ascertaining breast-feeding via questionnaire from mothers enrolled in the Framingham Study. The adult offspring were from the Framingham Third Generation Study and their mothers of the second generation. Body mass index (BMI), HDL cholesterol, total cholesterol, triglycerides, fasting blood glucose, and systolic and diastolic blood pressure levels were all obtained from 962 third generation subjects. The relationship between cardiovascular risk factors and maternal breastfeeding history was statistically determined and evaluated after adjusting for maternal and participant lifestyle, education, etc.

**Results:** Slightly more than half the participants were women, and one fourth of their mothers reported breastfeeding. There were modest but statistically significant differences in body mass index and HDL cholesterol levels between groups, with breastfeeding exerting a positive effect. The association between breastfeeding and HDL cholesterol was attenuated after adjustment for BMI, which may mediate the association between breastfeeding and HDL cholesterol levels. Breast-feeding was not associated with total cholesterol, triglycerides, fasting blood glucose, or blood pressure levels.

**Conclusions:** Breast-feeding in infancy, for at least 1 month, is inversely correlated with adult BMI, and is positively associated with HDL cholesterol levels.

**Reviewer’s Comments:** Here is an article that provides additional incentive to encourage breast-feeding in mothers of newborn children. There are psychologic benefits to breast-feeding for mother and baby. It reduces infant infections, and as outlined in this article, appears to protect against adverse health outcomes in adolescence and adulthood, particularly obesity, hypertension, cardiovascular risk factors, and diabetes, to name a few. The 4 million women annually in the U.S. who give birth should be strongly motivated to breast-feed their offspring. (Reviewer-Berel Held, MD).

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Keywords: Breast-Feeding, Cardiovascular Disease, Body Mass Index, HDL Cholesterol

Print Tag: Refer to original journal article
Breast-feeding is associated with a decreased risk of premenopausal breast cancer among women with a family history of breast cancer.

**Background:** Results from observational studies have suggested that breast-feeding is associated with a decreased risk of developing premenopausal breast cancer. However, results are inconsistent, and data from large prospective cohort studies are lacking. Prior studies have not taken into account measures of intensity of lactation such as duration of lactation, breast-feeding exclusively, and lactation amenorrhea.

**Objective:** To assess the association between lactation intensity and the risk of premenopausal breast cancer.

**Design:** Prospective cohort study.

**Methods:** Detailed lactation history, family history, and medical history were obtained from biennial questionnaires from parous women who participated in the Nurses’ Health Study II from 1997 to 2005. Cox proportional hazard models were used to determine the relative risk of breast cancer by lactation history, adjusting for established risk factors. The primary outcome was incident premenopausal breast cancer.

**Results:** 60,075 parous premenopausal women were eligible for participation in the analysis. Of these women, 90% were white; 87% reported that they had ever breast-fed. There were 608 cases of premenopausal breast cancer diagnosed during 357,556 person-years of follow-up, with a mean age at diagnosis of 46.2 years. A lower incidence of premenopausal breast cancer was found among women who had ever breast-fed than among women who had never breast-fed (adjusted HR, 0.75; 95% CI, 0.56 to 1.00). No significant association was found with duration of lactation, breast-feeding exclusively, or lactation amenorrhea. The association between ever breast-feeding and breast cancer was modified by having a first-degree relative who had breast cancer. In this group, compared to women who never breast-fed, the covariate-adjusted hazard ratio was 0.41 (95% CI, 0.22 to 0.75). No observed association was found among women who did not have a family history.

**Reviewer's Comments:** For women who have a first-degree relative with breast cancer, ever having breast-fed was associated with a 59% risk reduction for developing premenopausal breast cancer. The authors point out that this is comparable to the risk reduction attributed to taking prophylactic tamoxifen. Notably, the duration of lactation, breast-feeding exclusively, and lactation amenorrhea did not appear to be factors in the protective effect of breast-feeding. Further studies are needed to confirm these findings and to study the effects of breast-feeding on breast cancer risk in non-white women and in women with known BRCA mutations. I encourage all women to breast-feed. I will also go the extra mile to convince women who are not inclined to do so to reconsider, especially if they have a family history of premenopausal breast cancer. For some women, breast-feeding is seen as a lifestyle choice rather than a health behavior. It is important to emphasize that there appears to be a significant benefit even if they cannot breast-feed exclusively or can breast-feed for only a few months. (Reviewer-Elaine F. Sachter, MD).

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Keywords: Breast Cancer Prevention, Premenopause

Print Tag: Refer to original journal article
**Objective:** To assess the value of ultrasound (US) as a primary test for diagnosis of intussusception.

**Methods:** Starting in 2001, US was used at the University of Michigan Health System in Ann Arbor as the first-line test for suspected intussusception. Examinations done from 2001 to 2007 on children aged ≤10 years for intussusception were reviewed both for clinical data and radiographic findings. Based on ultimate outcomes, US results were classified as true positive, true negative, false positive, or false negative.

**Results:** 814 US studies for intussusception were performed; 112 studies (14%) were interpreted as positive for intussusception, of which 97 were subsequently confirmed by enema or surgery as true intussusception for a false-positive rate of 13%. Seven hundred studies were negative (86% of total); 698 were found to be true negatives, with only 2 false-negative results. The sensitivity and specificity of US for detecting intussusception were both approximately 98%. The positive-predictive value of the test was 87.0%, and the negative-predictive value was 99.7%.

**Conclusions:** US is an excellent test for detecting ileocolic intussusception; it is both highly sensitive and specific, and should be the first-line study to diagnose the condition.

**Reviewer's Comments:** The authors make a strong case that US should be the study of choice to rule out intussusception. It is an operator-dependent modality, and one might conjecture that the strong numbers are due solely to an institutional strength of pediatric radiologists at Michigan. The authors noted specifically that a large portion of studies were being interpreted on overnight and weekend shifts by residents and non-pediatric radiologists, meaning less-experienced radiologists. They also note that in 16% of cases, additional diagnostic findings were detected including patterns suggestive of necrotizing enterocolitis, appendicitis, or hydronephrosis. (Reviewer-Mark F. Ditmar, MD).

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Keywords: Pediatric Ileocolic Intussusception, Diagnostics, Ultrasound

Print Tag: Refer to original journal article
Use of Antipyretics After Immunization Lessens Fever, Immune Response

Effect of Prophylactic Paracetamol Administration at Time of Vaccination on Febrile Reactions and Antibody Responses in Children: Two Open-Label, Randomised Controlled Trials.

Prymula R, Siegrist C-A, et al:
Lancet 2009; 374 (October 17): 1339-1350

Use of paracetamol following immunization reduces the antibody response to several vaccine antigens.

**Background:** Although fever is a benign, self-limited side effect of vaccination, it often provokes concern and prompts use of prophylactic antipyretic medication. Few studies have assessed the effect of antipyretics on vaccine response.

**Objective:** To assess the effect of prophylactic paracetamol on febrile reactions and antibody responses following routine immunization.

**Design/Participants:** Multicenter study enrolling infants starting a primary vaccine series at age 9 to 16 weeks, with booster doses given at 12 to 15 months.

**Methods:** Doses of pneumococcal conjugate, DTaP, IPV, Hep B, and Hib vaccines were administered per routine schedules. Children were randomly assigned to receive paracetamol every 6 to 8 hours for the first 24 hours after vaccines or to receive no medication (including no placebo). Booster doses were given, with or without paracetamol, consistent with the original group assignment. Symptoms, including injection site reaction, irritability, somnolence and loss of appetite, were solicited from parents for 3 days following immunization. Temperature was measured at least twice daily. Antibody titers were obtained 1 month before and 1 month after primary and booster doses.

**Results:** 459 subjects received primary vaccines; 414 received booster doses. Fever >39.5°C was not common in either the paracetamol or non-paracetamol group after the primary vaccine dose (<1% vs 1%) or after the booster (2% vs 1%). Fewer children in the paracetamol group had fever ≥38°C when compared to those untreated (42% vs 66% after primary vaccination and 36% vs 58% after booster). After primary vaccination, all solicited symptoms were less likely in the paracetamol group. The need for medical attention did not differ between groups, and was rare overall. Before receiving the first vaccine dose, the paracetamol-treated group showed significantly lower mean antibody concentrations against all 10 pneumococcal serotypes, Hib antigens, and tetanus, diphtheria, and pertussis antigens. Approximately 96% of children reached seroprotective antibody concentrations for Hib, diphtheria, tetanus, 3 pertussis antigens, all but 2 pneumococcal serotypes, Hep B, and polioviruses 1, 2, and 3. Within each study group, fever had little effect on vaccine response. Paracetamol use produced the same effect whether children ultimately did or did not have fever.

**Conclusions:** Independent of its effect on fever, use of the antipyretic, paracetamol, and (acetaminophen) substantially reduces the antibody responses to several vaccine antigens.

**Reviewer's Comments:** It seems that a direct effect of paracetamol, rather than a temperature-dependent factor, is responsible for the reduced antibody response. One theory, proposed by the authors, is a direct effect on the early cell-mediated response (signaling between dendritic, T-cells, and B-cells). Since most children did achieve seroprotective levels, the effect seems modest. But, considering the lack of protection afforded by antipyretics, it is reasonable to discourage prophylactic use of acetaminophen after vaccines until the implications for individuals and public health are clarified. (Reviewer-Alyssa Siegel, MD).

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Keywords: Antipyretics, Paracetamol, Vaccines, Antibody Response

Print Tag: Refer to original journal article
In Bell palsy, treatment with corticosteroids plus antivirals might be superior to steroids alone.

**Background:** Bell palsy is common and is frequently associated with persistent facial weakness or contracture. HSV1 or reactivation VZV is a likely culprit. Steroids improve outcome, but the effectiveness of antiviral agents is not yet clear.

**Objective:** To better understand the optimal treatment of Bell palsy for the reduction of unsatisfactory facial recovery.

**Design:** Studies on the treatment of Bell palsy with steroids and/or antivirals were reviewed, and the importance of early treatment, duration of therapy, and optimal dose was evaluated.

**Methods:** This systematic review and meta-analysis identified randomized controlled trials comparing treatment with steroids and/or antiviral agents versus placebo. Facial recovery outcomes were also measured.

**Results:** 18 trials (2786 patients) were included. Analyses revealed a clear benefit of corticosteroids alone (RR, 0.69; number needed to treat, 11 subjects to benefit 1 person) but no benefit with antiviral treatment alone. A synergistic effect was demonstrated with corticosteroids plus antiviral agents compared to steroids alone (RR, 0.75 at borderline significance. Higher doses of steroids (average of approximately ≥65 mg daily of prednisone x 1 week) appeared more effective than lower doses. Neither steroids nor antiviral treatments were associated with increased risk of major adverse events.

**Conclusions:** Corticosteroids at fairly high doses appear to be safe and effective in reducing the risk of poor outcome in Bell palsy; antiviral agents, when dosed with steroids, might provide additional benefit.

**Reviewer’s Comments:** In cases of Bell palsy, there is fairly strong evidence of the benefit of treatment with corticosteroids. This study further suggests that adding an antiviral agent (eg, valacyclovir) to steroids may further reduce the risk for long-term unsatisfactory facial recovery. However, a very similar review from Harvard also published this month (in BMJ) did not find a statistically significant benefit from the addition of antiviral agents (although there was a trend toward benefit). It seems that the verdict is still out, and that more large randomized trials are needed. The cost of a week of an antiviral agent (approximately $150) is not inconsequential, and the absolute additional reduction in risk (if any) is fairly small. However, incomplete recovery from Bell palsy is fairly common and can be devastating. This article will help me educate my patients on the clear benefits of steroid therapy and the possible benefit of adding an antiviral agent, so together we can decide on the best individual treatment course. (Reviewer-Molly Blackley Jackson, MD).

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**Keywords:** Bell Palsy, Corticosteroids, Antivirals

**Print Tag:** Refer to original journal article
Topical treatment with diclofenac gel helps reduce pain in patients with hand osteoarthritis.

**Objective:** To assess the safety and effectiveness of diclofenac sodium gel in patients with primary hand osteoarthritis (OA).

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

**Participants:** The study population included 385 patients aged >40 years with symptomatic OA in their dominant hands and who had definite x-ray changes. Participants had to have used NSAIDs for at least 1 pain episode in the past, have significantly more pain in the dominant hand than the non-dominant hand, and to have endured a washout phase prior to trial beginning.

**Methods:** Acetaminophen, up to 4 g/day, was allowed during the study period of 8 weeks on an as-needed basis. Of patients, 198 used diclofenac gel 4 times a day to affected areas, and 187 used the vehicle alone in the same manner for the entire 8-week study period. Evaluation at 4, 6, and 8 weeks included OA pain intensity score and the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) score, which is a measure of pain, stiffness, and function, as well as use of rescue medication and global rating of disease activity.

**Results:** Overall, the treatment group experienced a reduction in pain intensity, AUSCAN score, and global disease activity of around 40% at 4 and 6 weeks. Withdrawals from the study occurred early, and most were related to excessive use of rescue medication in the first few weeks. Adverse events were noted in 52.0% of the treatment group and 43.9% of the placebo group (mainly headache and skin irritation). Mild gastrointestinal symptoms were noted in 7.6% of the treatment group and 3.7% of the placebo group.

**Reviewer's Comments:** A nice industry-sponsored trial of topical treatment for hand OA. Study participants were vigilant about applying the medication topically 4 times a day and maintaining this for the whole 8 weeks. Improvement in function occurred with pain relief. Adverse events were frequent but mild. Topical diclofenac gel is a useful treatment for pain relief in hand OA, especially in patients who cannot tolerate NSAIDs and pain medication. (Reviewer-Peggy Schlesinger, MD).

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Keywords: Hand Osteoarthritis, Diclofenac

Print Tag: Refer to original journal article
Alcohol Consumption Relates Inversely to CHD in Hypertensive Men

Relation of Alcohol Consumption and Coronary Heart Disease in Hypertensive Male Physicians (From the Physicians’ Health Study).

Britton KA, Gaziano JM, et al:

Am J Cardiol 2009; 104 (October 1): 932-935

There is an inverse relationship between alcohol consumption and coronary heart disease in hypertensive men.

Background: Moderate drinking has been associated with a decreased risk of cardiovascular disease. There is, however, limited information on the association between alcohol consumption and coronary heart disease (CHD) in patients with hypertension. Alcohol has varying effects on the cardiovascular system, including possible beneficial effects on lipid profile and a reduction in blood pressure. However, increasing amounts of alcohol consumption have been shown to increase blood pressure. Hypothesis: Moderate alcohol consumption decreases the risk of myocardial infarction (MI) in patients with hypertension.

Methods: The study analyzed data from the Physicians’ Health Study, which was a randomized trial that examined the use of low-dose aspirin and beta-carotene for the primary prevention of cardiovascular disease and cancer in 22,071 male physicians from the United States with no history of MI. Data from 5164 participants with self-reported hypertension, who were apparently healthy and free of CHD at baseline, were analyzed. Incident MI was evaluated by annual follow-up questionnaires with subsequent validation via medical records.

Results: There were 623 cases of MI during the period 1982 to 2008. Compared with subjects consuming <1 drink per week, the hazard ratios for MI were 1.05, 0.78, and 0.57 for alcohol consumption of 1 to 4, 5 to 7, and >8 drinks per week, respectively, after adjusting for age, body mass index, smoking, exercise, diabetes, multivitamin use, vegetable intake, breakfast cereal intake, and cholesterol. The P value for linear trend was <0.0022. Also, similar inferences about the protective effect of alcohol could be made for the secondary outcomes of the study, including angina pectoris and total CHD (MI, angina pectoris, and previous revascularization).

Conclusions: The study demonstrated a significantly inverse relationship between moderate alcohol consumption and coronary heart disease in hypertensive men. There was also a similar protective relationship seen between alcohol consumption and angina pectoris and total coronary heart disease.

Reviewer’s Comments: There are numerous studies that have demonstrated a strong relationship between alcohol consumption and a decreasing incidence of CHD. This protective effect appears to be similar in both men and women, regardless of geographic area or ethnic grouping. This protective effect may be due to the beneficial effects alcohol has on the blood lipid profile as well as on reducing platelet aggregation, increasing fibrinolysis, reducing blood insulin levels, and reducing coronary artery spasm in response to stress. This study suggests a decreased risk of cardiovascular disease with moderate alcohol consumption even in those patients who have hypertension at baseline. This may be since although alcohol itself has been shown to increase blood pressure, this negative effect is largely blunted by alcohol’s effects on platelet aggregation, inflammation, and insulin sensitivity in moderate drinkers. (Reviewer-Suraj Maraj, MD).

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Keywords: Alcohol, Coronary Heart Disease, Hypertension

Print Tag: Refer to original journal article
Screening reduces the risk of death from colorectal cancer, but different methods have different benefits and risks. Colonoscopy is the preferred screening method recommended by the American College of Gastroenterology.

Objective: To review formal guidelines and make clinical recommendations on screening for colorectal cancer. Results: Screening significantly reduces the risk of death from colorectal cancer. A number of screening methods and strategies are available. Fecal occult blood guaiac tests are low-cost, noninvasive tests that can be performed at home. When performed in triplicate, they have a sensitivity of 50% to 75% for detecting cancer. Fecal immunochemical tests employ antibody reagents and may be more sensitive, but have reported variable performances. Patient compliance with testing, compliance with follow-up colonoscopy, and costs of follow-up colonoscopy make the cost of screening by fecal occult blood testing similar to colonoscopy screening. Stool DNA tests that employ polymerase chain reaction (PCR) amplification for colorectal cancer-associated mutations are improving toward more sensitive, second-generation assays that remain unproven with respect to sensitivity, cost, screening interval, and management recommendations. This may be a promising future method for colorectal cancer screening and is recommended by the American Cancer Society, but is not recommended by the U.S. Preventive Services Task Force. CT colonography is 90% sensitive for detecting polyps ≥10 mm with a false-positive rate of 14%, but is less accurate for polyps <6 mm and has unproven predictive value in routine practice. It is recommended by the American Cancer Society, but not by the U.S. Preventive Services Task Force. Colonoscopy outcomes have not been effectively compared to other screening methods. In the U.S., sigmoidoscopy (distal only) is limited by its inaccessibility to proximal lesions and by patient discomfort. Colonoscopy is the preferred screening method recommended by the American College of Gastroenterology, but has room for improvement, especially in its false-negative detection of flat adenomas. Significant bleeding or perforation is uncommon, occurring in 0.3% to 0.5% of colonoscopies.

Conclusions: Screening reduces the risk of death from colorectal cancer, but different methods have different benefits and risks. Colonoscopy is the preferred screening method recommended by the American College of Gastroenterology.

Reviewer's Comments: Screening recommendations for different populations may vary. For example, blacks may benefit from screening at age 45 years as opposed to age 50 years. Colonoscopy is not generally recommended after age 75 years but may be indicated in persons with no previous screening. (Reviewer-Guy E. Nichols, MD, PhD).

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Keywords: Colorectal Cancer, Colonoscopy, Fecal Testing

Print Tag: Refer to original journal article
Breast Cancer Imaging Is Continuously Improving

Image-Detected Breast Cancer: State-of-the-Art Diagnosis and Treatment.

Silverstein MJ, Recht A, et al:

J Am Coll Surg 2009; 209 (October): 504-520

This consensus panel statement provides up-to-date information on image-detected breast cancer, including economic issues relative to treatment and diagnosis.

**Objective:** To address issues, available evidence, and implications of recommendations for diagnosis and treatment of image-detected breast cancers.

**Design:** Consensus conference report.

**Participants:** Interdisciplinary physicians specializing in the diagnosis and treatment of breast disease.

**Methods:** Challenging issues relative to breast diagnostic imaging were presented to a panel for discussion and updated consensus opinion formulation. The panel used information from previous basic concepts acquired during a 2001 and 2005 consensus conference. The panel discussed modes of diagnosis and treatment, but this particular report was directed primarily at addressing state-of-the-art diagnosis and treatment associated with imaged-detected breast cancer.

**Results:** There was a general statement from the panel regarding the lack of standardization of digital breast imaging and the panel encouraged a standardization of format by the manufacturers of digital equipment. They reaffirmed that mammography is the only imaging modality that is currently recommended for routine screening. Digital mammography offers the advantage of a slightly lower radiation dose, reduced cost of archiving, ease of retrieval, and the ability to transmit studies through electronic networks. However, there has been no demonstrated difference in the cancer detection rate between analog and digital mammography. Computer-aided detection can increase rate of cancer detection in both screening and diagnostic populations. Breast ultrasonography is commonly used to characterize lesions that are detected through mammograms, but routine screening with breast ultrasonography is not currently recommended. Breast MRI is used more frequently, but this panel concluded that MRI can be useful as a screening modality for patients at high risk for breast cancer. They also advised that MRI should not be used as a replacement for diagnostic mammography or ultrasonography. Breast-specific gamma imaging or positron emission mammography can be used as an alternative to breast MRI if MRI is not available. There was agreement by the panel that percutaneous needle biopsy has accuracy that is equivalent to open surgical biopsy. The consensus panel also encouraged standardized grading and size determination for pathologic specimens and commented on the importance of tumor size and margin assessment, along with tumor markers. The panel also reaffirmed that the substantial body of evidence showing that sentinel lymph node biopsy for axillary staging is accurate and causes less morbidity than axillary dissection.

**Conclusions:** This consensus panel statement provides up-to-date information on image-detected breast cancer, including economic issues relative to treatment and diagnosis.

**Reviewer's Comments:** This manuscript is worthy of attention by practicing gynecologists in that it gives a very good summary of current methodology for diagnosis and treatment of breast cancer. Breast diagnosis remains a challenge for gynecologists, but a knowledge of this aspect of health care for women is a must for the gynecologist. (Reviewer-John C. Jennings, MD).

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Keywords: Breast Cancer, Diagnosis, Treatment

Print Tag: Refer to original journal article
Psychotropic Drug Use in Breastfeeding, Risks to Infants--An Update

Fortinguerr F, Clavenna A, Bonati M:

Pediatrics 2009; 124 (October): e547-e556

Updated information concerning psychotropic drug use and breastfeeding helps elucidate which drugs may be better to prescribe to breastfeeding mothers.

**Background:** While breastfeeding is strongly encouraged for most mothers, there is hesitancy to recommend it for women taking psychotropic medications due to the paucity of safety information concerning the infant.

**Objective:** To review current literature pertaining to psychotropic medications and breastfeeding to provide updated information on exposure levels and risks to infants.

**Design:** Literature review.

**Participants:** Breastfeeding mothers and their infants. Mothers were taking 1 of 96 psychotropic medications.

**Methods:** Original articles and review articles were identified through MEDLINE, Embase, and PsychINFO. Additionally, secondary sources such as reference books were reviewed. Articles and texts included in the analysis had to address pharmacokinetic data and adverse effects in infants. Of the articles included, the following information was abstracted: maternal dosage, number of mother-infant dyads, milk-to-plasma drug ratio, relative infant dosage, and incidence of infant adverse events. Using this information, each drug was then categorized as compatible, to be used with caution, or contraindicated.

**Results:** 62 of 96 drugs had information available for review. Of these, the greatest amount of information existed for antiepileptic medications. Valproate and carbamazepine were found to be compatible because of their low excretion and adverse events rates. Similarly, sertraline, paroxetine, and fluvoxamine were considered compatible antidepressants, and chlorpromazine and olanzapine were compatible antipsychotics. Due to lack of information, all anti-anxiolytics were labeled as “use with caution,” but the investigators added that due to infants’ slower metabolism, short-acting benzodiazepines were likely better because they were less likely to build up. Psychostimulants could not be categorized due to lack of information. With all medications reviewed, the investigators stressed that the risks of the drugs must be viewed in light of the benefits of breastfeeding as well as the mental health needs of the mother and the benefits gained by being properly medicated.

**Conclusions:** This study was able to update safety information on 62 of 96 psychotropic medications and provide some recommendations concerning which drugs are safer to use during breastfeeding.

**Reviewer’s Comments:** This article provides a nice, clean summation of what is known about the risk to breastfed infants from exposure to psychotropic medications, thereby allowing pediatricians to better counsel breastfeeding mothers. As stressed by the investigators, this information is still incomplete, and more research is needed to best advise mothers as they balance the needs of their infants and their own mental health needs. (Reviewer-Lisa Humphrey, MD).

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Keywords: Psychotropic Drug Use, Breastfeeding

Print Tag: Refer to original journal article
The N95 respirator has the same results in preventing influenza in nurses as standard surgical masks.

**Objective:** To compare the N95 respirator to the standard surgical mask in preventing confirmed influenza in nurses in a hospital setting.

**Methods:** Full-time nurses were enrolled in emergency department, medical units, and pediatric units in 8 tertiary hospitals in Ontario, Canada. Nurses were randomized to receive either the regular hospital-supplied surgical mask or N95 respirator when they were within 1 meter of contact with a febrile patient with cough or shortness of breath. Nurses were assessed via web questionnaires every 2 weeks concerning their health status. If new symptoms occurred, a nasal swab was obtained for culture, and blood testing was performed. N95 respirator masks were fitted for a majority of the nurses. The outcome was to determine the incidence of laboratory-confirmed influenza in these 2 groups. This study took place from September 23, 2008, to December 8, 2008.

**Results:** 446 nurses were enrolled, with 225 in the surgical mask group and 221 in the N95 respirator group. Influenza vaccination status was the same between groups with 30% in the surgical-mask group and 28% in the N95 respirator group with the 2008 to 2009 trivalent-inactivated influenza vaccine. Laboratory-confirmed influenza by PCR in serum occurred in 50 nurses (23.6%) in the surgical-mask group and 48 nurses (22.9%) in the N95 group. The study also noted that 8.0% in the surgical mask group had H1N1 versus 11.9% in the N95 group. Of nurses, 25% in the surgical mask group reported an exposure to a spouse or roommate with influenza-like illness compared to 22% in the N95 group.

**Conclusions:** The N95 respirator had the same results in preventing influenza in nurses as did standard surgical masks.

**Reviewer's Comments:** This article shows that there were no significant differences between these 2 masks. Some of limitations include the lack of data on glove wearing, hand washing, and gown wearing. The authors commented that N95 respirators are superior to the mask and should be considered in highly infectious individuals; however, in an outpatient clinic setting, surgical masks may be just as protective in preventing influenza. The exposure to sick contacts outside the hospital may have had an effect on the infection rates in these 2 groups. (Reviewer-Charles I. Schwartz, MD).

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**Keywords:** Protective Respiratory Masks, Surgical Masks, Influenza

**Print Tag:** Refer to original journal article
The combination of pharmacotherapy and psychotherapy appears to be more effective than either method alone in the treatment of depression.

Background: The effect sizes from previous studies investigating the relative value of combined pharmacotherapy and psychotherapy for the treatment of depressive disorders have been small, although they are generally in favor of combined treatment. 

Objective: To better determine the statistical significance of these findings using meta-analytical statistical methods, as well as to explore whether certain study characteristics are related to relative effects of pharmacologic and combined treatment.

Methods: From the available literature, the study selection was narrowed down to 25 studies that met inclusion criteria of using randomization to determine the effects of combined treatments in depression, resulting in a total of 2036 patients. Eight studies examined cognitive behavioral therapy (CBT), another 8 examined interpersonal therapy, and 9 examined other psychological treatments, such as psychodynamic therapy or problem-solving treatment. Selective serotonin reuptake inhibitor (SSRI) treatments were examined in 9 studies, tricyclic antidepressants (TCAs) were evaluated in 9 studies, and other medication protocols were evaluated in the remaining 7 studies. The authors then carefully examined whether one of the studies with the larger number of subjects had an impact that skewed the results by removing a few studies 1 at a time and rechecking the results each time. Subgroup analyses were also conducted to more carefully investigate the heterogeneity between the studies.

Results: The mean effect size indicating the difference between pharmacotherapy and combined therapy was 0.31, which, although small, was statistically significant due to the large collective sample size. The number needed to treat was 5.75. Heterogeneity was low to moderate between studies. Subgroup analyses revealed that studies aimed at patients with dysthymia resulted in significantly lower effect sizes. Psychotherapy had an additive effect for both TCAs and SSRIs, with no significant differences between medication classes. Dropout rates were significantly lower with combined treatment versus pharmacotherapy alone.

Conclusions: Combined pharmacotherapy and psychotherapy appears to be more effective for depression, no matter whether TCAs or SSRIs are used, with the possible exception of lower efficacy in general and lack of combined treatment benefit for patients with dysthymia.

Reviewer's Comments: This meta-analysis is somewhat reassuring, and very much needed, as the effect sizes for the individual studies are typically small and show little difference between combined treatment and medication alone. However, if one looks at the included studies side by side, one can still see that the trials in aggregate are, unfortunately, not a compelling set. (Reviewer-John G. Koutras, MD).

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Keywords: Depression, Cognitive Behavioral Therapy, Antidepressants

Print Tag: Refer to original journal article
In this article, the rise in melanoma incidence was almost exclusively stage 1 disease.

**Background:** It is stated that excessive ultraviolet light exposure has led to an increased incidence of melanoma in the United States and in the world. Over the years, that alarmist warning has been challenged--there are some who believe it is a reporting artifact. One of the strongest arguments for this opposing view is the observation that there has been a huge rise in melanoma over the past 2 decades without a corresponding rise in death rates from melanoma.

**Objective:** To analyze changes in melanoma incidence, stage, and mortality in the eastern United Kingdom.

**Design:** Retrospective review.

**Participants:** 3971 patients diagnosed with malignant melanoma between 1991 and 2004 were part of the study; melanoma in situ patients were excluded.

**Results:** The authors found the melanoma incidence rate increased continuously each year from 9.39 to 13.91 cases/100,000 population per year. On the other hand, mortality rates increased only from 2.16 to 2.54 cases/100,000 population per year, and thus, the ratio of change in incidence-to-mortality of 12:1. There were 2192 deaths due to melanoma in the study population. When looking at the types of melanoma that were being diagnosed, the authors found that the rate of stage 1 melanomas showed an increase of 4.81 to 8.98 cases/100,000 population per year, with no increase in the other stages when taken as a group (although there was a slight increase in stage 2 and a slight decrease in stage 4 melanomas in subgroup analysis). The prognosis for the stage 1 cases was excellent, effectively 100% for the study group.

**Conclusions:** In their conclusion, the authors offered 2 possible explanations for their findings. The first was that there really was an increase in incidence of genuine, potentially fatal malignant melanoma. They argued that this was improbable given the unlikelihood that public education and early detection was so successful as to limit the increase to stage 1 disease. They favored the alternative explanation, which was that the large increase in incidence was not due to a true malignant melanoma, but rather a change in histopathological diagnosis criteria defining the disease. They postulated that simple or dysplastic nevi that were in fact benign are now being reclassified as stage 1 melanoma. They proposed that until the necessary research is done, encouragement of public anxiety about a melanoma epidemic and excessive avoidance of solar exposure for its prevention is unjustifiable.

**Reviewer's Comments:** This article obviously came with some attitude and bias built into it. Unfortunately, I do not see a resolution to the questions this article and others bring up. You will never see an Institutional Review Board approving any study that says we will not remove lesions with the pathologic diagnosis of invasive malignant melanoma. (Reviewer—David L. Swanson, MD).

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Keywords: Melanoma, Diagnosis, Epidemiology, Risks

Print Tag: Refer to original journal article
Objective: To evaluate percutaneous peripheral tibial stimulation for overactivity in patients with overactive bladder.

Design: Randomized, multicenter controlled study.

Methods: Patients with typical overactive bladder symptoms who were undergoing either treatment with percutaneous tibial nerve stimulation or extended-release tolterodine for 3 months of therapy were evaluated. It was a 1:1 randomization study. Voiding diaries, as well as overactive bladder questionnaires were used at baseline and at end of therapy to compare overall symptoms after interventions. Results of treatment were measured in terms of reduction in urinary frequency on a 24-hour basis, urinary urge incontinence episodes on a 24-hour basis, urgency episodes, as well as quality-of-life indices. There was also a global response questionnaire completed by subjects and investigators at 12 weeks of therapy. Percutaneous tibial stimulation was done in standard fashion as previously described, using peripheral nerve stimulation. Pharmacotherapy was done with extended-release tolterodine.

Results: Overall, global response instruments showed significant improvement in percutaneous tibial stimulation averaging 79.5% reporting cure or improvement as compared to 54.8% of patients on tolterodine. This was highly statistically significant. Diary-based variables also showed improvements in urge incontinence, urge episodes, volume voided, and voids per day that were more significant with tibial stimulation as compared to extended-release tolterodine. Rather statistically significant decreases were noted across all overactive bladder parameters except for volume voided. There were no serious adverse events in either group.

Conclusions: In this trial, tibial nerve stimulation was safe and generated statistically significant improvements in patients.

Reviewer’s Comments: Percutaneous tibial nerve stimulation was more effective than oral drug therapy in this trial in using both objective and subjective measures. There was also significant objective benefit with this as compared to oral pharmacotherapy, and the authors felt that this could be representative of an alternative therapy for overactive bladder. (Reviewer-Roger Dmochowski, MD).

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Keywords: Electric Stimulation Therapy, Tibial Nerve, Tolterodine, Urinary Incontinence

Print Tag: Refer to original journal article