

Long-term erythromycin therapy decreases COPD exacerbations

Clinical question Does the long-term use of erythromycin reduce exacerbations in patients with moderate to severe chronic obstructive pulmonary disease (COPD)?

Bottom line In patients with moderate to severe COPD, twice daily erythromycin reduced the frequency of exacerbations and had a similar rate of adverse side effects as placebo at the end of 1 year. (Level of evidence = 1b)

Synopsis To be included in this study, patients had to have moderate to severe COPD based on spirometry and not have used antibiotics or corticosteroids during a run-in period. Unlike other studies where patients receive study medication during the run-in period to weed out patients who are nonadherent or unable to tolerate the medication, the run-in period for this study was used merely to ensure that the patients had no exacerbations before baseline data were collected. Patients were randomized to receive 250 mg erythromycin twice daily (n = 53) or placebo (n = 56) for 12 months. In addition to physiologic data, the patients also kept track of the number of moderate or severe exacerbations. A moderate exacerbation of COPD was defined as sustained worsening of symptoms for at least 2 days treated with antibiotics, corticosteroids, or both. A severe exacerbation was defined as those resulting in hospital admission. Exacerbations were evaluated by a researcher unaware of the patient's treatment group assignment. The researchers used intention to treat to assess the outcomes. By the end of 12 months, nine patients treated with erythromycin withdrew from the study compared with 10 treated with placebo (one of whom died). The two treatment

groups were similar at baseline. Among patients treated with erythromycin, there were 81 moderate to severe exacerbations compared with 125 in patients treated with placebo. The median frequency of exacerbations was two for patients taking placebo and one for patients taking erythromycin. The median time to the first exacerbation was also longer in patients taking erythromycin (271 days vs 89 days). The duration of exacerbations was also shorter in the erythromycin group: 13 days (95% CI, 16-24) versus 9 days (6-14). Although there were 6 hospitalizations (7.4%) in patients treated with erythromycin compared with 14 (11.2%) for patients treated with placebo, the study lacked power to detect meaningful differences in this outcome. There were no differences in adverse effects in either group.

Seemungal TA, Wilkinson TM, Hurst JR, et al. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med.* 2008;178(11):1139-1147.

ACP guideline: New antidepressants are similarly effective

Clinical question Of the new (non-cyclic) antidepressants, which one should be used first in patients with major depressive disorder?

Bottom line Citing similar effectiveness and effect on quality of life, this guideline from the American College of Physicians (ACP) recommends choosing a second-generation antidepressant on the basis of factors other than effectiveness. They suggest selecting an antidepressant according to its side effect profile, cost, and patient preference; not by mechanism of action or presumed differences in effectiveness. Mirtazapine (Remeron) has been found to have a faster onset in the first 2 weeks, but this difference disappears by the fourth week. The guidelines also point out that a significant number—almost half—of patients will not respond to the first antidepressant selected and that only 1

in 4 who are switched to a second antidepressant will respond. (Level of evidence = 1a)

Synopsis To develop this guideline, the ACP commissioned a systematic review of the literature comparing the newer antidepressants, such as the selective serotonin reuptake inhibitors, norepinephrine reuptake inhibitors, and selective serotonin norepinephrine reuptake inhibitors. Searching five databases, including the Cochrane Registry, the authors identified 80 English language head-to-head randomized controlled trials enrolling more than 17,000 patients. Studies were independently selected by two researchers, conducting meta-analyses when the data could be combined. The group found moderate evidence supporting equivalence among the second-generation antidepressants with regard to comparative efficacy, effectiveness, quality of life, and maintaining response. Mirtazapine has a faster onset of action, producing a significantly better response after 2 weeks of treatment, though the difference disappears by week 4. Anxiety responds well to any antidepressant. The authors did not locate research allowing them to conclude whether any antidepressant is better than any other at controlling melancholia, pain, or insomnia. Venlafaxine (Effexor) is more likely to cause nausea, sertraline (Zoloft) causes more diarrhea, and mirtazapine is associated with weight gain. Bupropion is less likely to cause sexual dysfunction.

Qaseem A, Snow V, Denberg TD, et al; Clinical Efficacy Assessment Subcommittee of American College of Physicians. Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2008;149(10):725-733.
Gartlehner G, Gaynes BN, Hansen RA, et al. Comparative benefits and harms of second-generation antidepressants: background paper for the American College of Physicians. *Ann Intern Med.* 2008;149(10):734-750.

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High dose statin reduces cardiac events in patients with high CRP

Clinical question In patients with normal LDL cholesterol but elevated C-reactive protein (CRP), is a high-dose statin effective for primary cardiovascular prevention?

Bottom line In this study of patients with normal LDL and elevated CRP, use of a high-dose statin reduced the risk of death over a 2-year period (number needed to treat [NNT] = 180). At a cost of approximately \$1,200/y for rosuvastatin, the cost per life saved is about \$216,000. This study raises many questions. What is the long term safety of lowering LDL cholesterol to 55 mg/dL in otherwise healthy persons? What is the impact of the apparent increase in diabetes on the long-term benefit of this drug? Can less expensive statin drugs, perhaps at lower doses, provide a similar benefit with less risk? (Level of evidence = 1a)

Synopsis The Air Force/Texas Coronary Atherosclerosis Prevention Study found that statins may be effective in patients with normal cholesterol but elevated levels of CRP, a measure of inflammation. In this study, the authors identified adults with LDL cholesterol less than 130 mg/dL and CRP higher than 2.0 mg/L. Nearly 90,000 men over age 50 years and women over age 60 years were screened for enrollment in the trial, and the vast majority were excluded because of an elevated LDL (37,611), low CRP (25,993), withdrawal of consent (3,948), diabetes (957), hypothyroidism (349), or other reasons. Patients with preexisting heart disease or who had ever taken a statin or hormone replacement therapy were ineligible, as were patients with elevated creatine kinase, creatinine, or hepatic transaminases at baseline. The remaining 19,323 patients took placebos for 4 weeks to assess their compliance, and those taking less than 80% of the study drug were excluded. This of course has the effect of making the

study drug look more effective than it is in the real world of clinical practice. The remaining 17,802 patients (62% male, 75% white, mean age 66 years) were randomized to rosuvastatin (Crestor), 20 mg once daily, or matching placebo. At each of the annual follow-up visits, the LDL in the rosuvastatin group was approximately half that of the placebo group (55 vs 110 mg/dL) and the CRP was also significantly lower (~2.0 vs 3.5 mg/L). The study was terminated early after 1.9 years of median follow-up. At that time, all cause mortality was lower in the rosuvastatin group (1.0 vs 1.25 per 100 patient years, $P = .02$). There was a consistent pattern of fewer cardiovascular events for patients taking rosuvastatin, including fewer MI (0.17 vs 0.37 per 100 patient years, $P = .0002$) and fewer strokes (0.18 vs 0.34 per 100 patient years, $P = .002$). Patients taking rosuvastatin were more likely to be diagnosed with diabetes mellitus (270 vs 216 cases, $P = .01$). There was only one reported case of rhabdomyolysis, which occurred in a patient taking rosuvastatin.

Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195-2207.

Antispasmodics, peppermint effective for IBS

Clinical question What treatments relieve symptoms in patients with irritable bowel syndrome (IBS)?

Bottom line Fiber provides minimal likelihood of benefit in patients with IBS. Antispasmodics, particularly scopolamine (hyoscine) and otilonium, are effective in 50% to 70% of patients. Peppermint oil is also effective, with approximately 75% of patients responding (number needed to treat [NNT] = 2.5). (Level of evidence = 1a-)

Synopsis No one is throwing a lot of money at researchers to study treatment of this common but not-front-page-news problem in adults. As a result, the available research is incom-

plete and much of it was done many years ago. To conduct this meta-analysis, the researchers searched 3 databases, including the Cochrane Registry, to identify randomized controlled trials investigating the treatment of IBS. The studies could use any of several definitions of IBS and had to be a least 1 week in length (most were longer). Two reviewers independently selected the studies, abstracted the data, and evaluated study quality.

Most of the studies were small; meta-analysis overcomes this limitation but adds the risks of combining studies in different populations using different methods and evaluating different outcomes. This limitation was particularly evident in this analysis. Twelve studies evaluated the usefulness of fiber in a total of 591 patients, finding, overall, only minimal benefit, with this benefit erased when only higher-quality studies were evaluated. In 1,778 patients enrolled in 22 studies, antispasmodics were effective, though the study results were heterogeneous and there was evidence of publication bias. Only the antispasmodics scopolamine (hyoscine) and otilonium were consistently effective (NNT = 3-4.5). Peppermint oil has been evaluated in four studies of 392 patients. It was effective at doses of approximately 200 mg twice daily, with a NNT of 2.5 (95% CI, 2.0-3.0).

Ford AC, Talley NJ, Spiegel BM, et al. Effect of fibre, antispasmodics, and peppermint oil on the treatment of irritable bowel syndrome: systematic review and meta-analysis. *BMJ*. 2008; 337:a2313. doi:10.1136/bmj.a2313.

Ginkgo biloba is not effective in reducing risk of dementia

Clinical question Is Ginkgo biloba effective in reducing the risk of dementia in the elderly?

Bottom line This well-done study found no evidence of benefit for Ginkgo biloba in reducing the risk of dementia or cognitive decline in the elderly. (Level of evidence = 1b)

Synopsis Because of its antioxidant action, G biloba may be effective in

reducing the risk of dementia in the elderly. These investigators recruited 3,069 adults, 75 years or older (mean = 79.1 years), with either normal cognition or mild cognitive impairment (MCI). Criteria for diagnosis of MCI at baseline were based on international guidelines. Study participants randomly received (concealed allocation assignment) G biloba extract (120 mg twice daily) or matched placebo. Individuals assessing outcomes remained masked to treatment group assignment. Complete data were available for 94% of patients at 6 years. Using intention-to-treat analysis, there was no significant difference in the incidence of total dementia—as defined using standard DSM-IV criteria—between the active treatment group and the control group (17.9% vs 16.1%, respectively). Of the total dementia cases, 92% were specifically classified as Alzheimer's dementia (AD); the rate of AD did not significantly differ between the two groups. There were also no significant differences between the two groups in adverse events, major bleeding events, or all-cause mortality. G biloba did not significantly reduce the rate of progression to dementia among patients with MCI at baseline. The study was 86% powered to detect a 25% difference in dementia between the two treatment groups.

DeKosky ST, Williamson JD, Fitzpatrick AL, et al; Ginkgo Evaluation of Memory (GEM) Study Investigators. Ginkgo biloba for prevention of dementia: a randomized controlled trial. *JAMA*. 2008;300(19):2253-2262.

Clinical rule identifies patients at low risk of recurrent VTE

Clinical question Can a combination of clinical and laboratory findings identify patients at low risk of recurrent venous thromboembolism (VTE)?

Bottom line After 6 months of anticoagulation for an initial unprovoked

deep vein thrombosis (DVT) or pulmonary embolism (PE), a clinical rule can identify approximately half the women at low risk for recurrence (<2%). A similar rule can also identify men at moderately low risk (<4%). High-risk women (14.1% annual recurrence risk) and men (18.8% annual recurrence risk) should strongly consider continued anticoagulation. A previous study found that a normal D-dimer value 3 weeks after discontinuing anticoagulation also predicts low risk of recurrence (*JAMA*. 2003;290[8]:1071-1074). (Level of evidence = 2b)

Synopsis Current guidelines recommend anticoagulation for 6 months in patients with an initial unprovoked episode of DVT or PE, but recurrence after discontinuation of warfarin occurs in 5% to 27% of patients in the first year, 5% in the second year, and approximately 2% to 4% in each year after that. Of course, this risk must be balanced against the risk of a major bleed while anticoagulated, which is approximately 2% to 3% per year. Identifying patients who are at high risk for recurrent thrombosis (and, ideally, at low or average risk of bleeding problems) is therefore an important goal. In this study, the researchers identified 646 patients with a first unprovoked episode of VTE who had been treated with an oral anticoagulant for 5 to 7 months. Patients with known thrombophilias or recurrence during the period of anticoagulation were excluded. Patients had their initial assessment for 69 potential predictors of recurrence while still completing their course of anticoagulation (a limitation of a previous study that used D-dimer testing to predict recurrence was that patients had to be off anticoagulants for at least 1 month). Of the initial study group, 600 were followed up for a mean of 18 months (range = 1 to 47 months). The mean age of patients

was 53 years (range = 18 to 95 years) and 49% were women; the initial event was DVT for 53%, PE for 30%, and both for 17%. The annualized risk of recurrence was 13.7% for men and 5.5% for women, and the variables associated with recurrence on univariate analysis differed somewhat between men and women. A number of candidate clinical decision rules were developed and tested for men and women. For women, there were five key independent predictors in the best-performing model: hyperpigmentation; edema or redness of either leg; D-dimer result 250 µg/L or more; body mass index greater than or equal to 30 kg/m²; and age 65 years or older. The annual risk of recurrent VTE was 1.6% among women with 0 or 1 risk factors, compared with 14.1% among women with 2 or more risk factors (positive likelihood ratio = 2.0; negative likelihood ratio = 0.2). A rule consisting of 3 independent predictors (hyperpigmentation; edema or redness of either leg; antiphospholipid antibody level higher than 6 U/mL; and hemoglobin level 170 g/L or higher) performed less well, with an annual risk of recurrent VTE of 3.7% in the low-risk group (0 or 1 predictors) and 18.8% in the high-risk group. The authors discount the rule for men as unhelpful because of the higher risk of recurrent VTE in the low-risk group; however, it may still be useful, particularly in men at higher-than-average risk for bleeding complications or those who wish to avoid anticoagulation for other reasons.

Rodger MA, Kahn SR, Wells PS, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. *CMAJ*. 2008;179(5):417-426.

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