

Carbamazepine effective for alcohol withdrawal

Malcolm R, Myrick H, Roberts J, Wang W, Anton RF, Ballenger JC. The effects of carbamazepine and lorazepam on single versus multiple previous alcohol withdrawals in an outpatient randomized trial. *J Gen Intern Med* 2002; 17:349-55.

■ **BACKGROUND** Outpatient management of symptoms from acute alcohol withdrawal usually includes a tapering regimen of a benzodiazepine such as lorazepam (Ativan). Benzodiazepine use is usually limited, however, by the potential for medication abuse and side effects such as central nervous system impairment. Because studies have demonstrated that carbamazepine can be effective for the treatment of alcohol withdrawal symptoms, this study compared the effectiveness of carbamazepine with that of lorazepam.

■ **POPULATION STUDIED** The 136 patients were self-referred and fulfilled *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria for alcohol dependence and alcohol withdrawal. Patients lived within 50 miles of the study site, and had an admission blood alcohol level < 0.1 g/dL, a Mini Mental State Examination score of ≥ 26 , and an admission score on the Clinical Institute Withdrawal Assessment-Alcohol, revised (CIWA-Ar) ≥ 10 out of a possible score of 20. Patients were excluded if they had substance abuse syndromes other than alcohol dependence, nicotine dependence, or cannabis abuse; major Axis I psychiatric disorder; used benzodiazepines, beta-blockers, calcium channel blockers, or antipsychotic agents within the past 30 days; a history of head injury; neurologic illness; or grossly abnormal laboratory values.

■ **STUDY DESIGN AND VALIDITY** This was a randomized double-blind trial comparing 2 different treatments for alcohol withdrawal. Allocation to treatment group was concealed from enrolling physicians. The patients received a 5-day taper of either lorazepam 6-8 mg tapered to 2 mg or carbamazepine 600-800 mg tapered to 200 mg. Withdrawal symptoms were measured using a validated CIWA-Ar tool. Patients also completed a daily drinking log to assess alcohol use prior to, during, and 7 days after study completion. The study evalu-

ated 89 patients after the treatment period for number of drinks taken per day.

This well-done study had several limitations. This study relied on self-referral by patients who reported previous withdrawal episodes. Most patients were white middle-aged men, and the results may not be the same in other populations.

■ **OUTCOMES MEASURED** Alcohol withdrawal symptoms and posttreatment alcohol use measured by the CIWA-Ar scale were the primary outcomes. Side effects were reported as a secondary outcome.

■ **RESULTS** Both drugs were equally effective in reducing alcohol withdrawal symptoms. Over time, alcohol withdrawal symptoms were more likely to occur with lorazepam treatment ($P = .007$). After treatment, relapsing patients receiving carbamazepine had fewer drinks per day than those receiving lorazepam (1 vs 3; $P = .003$). Effectiveness varied based on whether patients had attempted alcohol detoxification in the past. Of the patients who reported prior multiple detoxifications, those receiving carbamazepine drank less than 1 drink per day as compared with 5 drinks per day in the lorazepam-treated group ($P = .004$). The overall frequency of side effects were the same for both groups; however, clinicians recorded dizziness and incoordination in more patients on lorazepam than carbamazepine (22.7% vs 6.9%; $P = .02$). Pruritus occurred more often in the carbamazepine group than the lorazepam group (18.9% vs 1.3%; $P = .004$).

RECOMMENDATIONS FOR CLINICAL PRACTICE

Carbamazepine is an effective alternative to benzodiazepines for the outpatient treatment of alcoholic withdrawal symptoms. Carbamazepine appears to be particularly effective for patients in whom detoxification failed in the past.

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Inhaled fluticasone superior to montelukast in persistent asthma

Meltzer EO, Lockey RF, Friedman BF, et al. Efficacy and safety of low-dose fluticasone propionate compared with montelukast for maintenance treatment of persistent asthma. *Mayo Clin Proc* 2002; 77:437-45.

■ **BACKGROUND** Asthma management guidelines recommend patients with persistent asthma use asthma controller therapy in addition to as-needed short-acting beta-agonist therapy to improve symptom control, maintain pulmonary function, and decrease exacerbations. This study compared 2 asthma controllers, inhaled fluticasone and oral montelukast, with respect to clinical efficacy, patient preference, asthma-specific quality of life, and safety.

■ **POPULATION STUDIED** The patients in this study were men and women aged 15 years and older with asthma recruited from multiple centers across the United States. Nonsmoking patients were included with a forced expiratory volume in 1 second (FEV₁) of 50% to 80% of predicted that reversed by at least 15% with bronchodilator use. Patients were then eligible for randomization if, after an 8- to 14-day run-in period, their FEV₁ remained within 15% of initial values, they used albuterol at least 6 of the last 7 days, and they had asthma symptom scores of ≥ 2 (on a 0 to 5 scale) for at least 4 of the last 7 days.

■ **STUDY DESIGN AND VALIDITY** This study was a double-blinded, randomized trial sponsored by the makers of fluticasone. Patients meeting initial inclusion criteria underwent an 8- to 14-day run-in period in which only short-acting beta-agonist use was allowed. Patients were then randomized to 1 of 2 treatment groups if they met the secondary inclusion criteria. Personal communication with the lead author confirmed that allocation assignment was concealed. Patients received either fluticasone 88 μ g twice daily via metered dose inhaler (MDI) and montelukast placebo, or montelukast 10 mg daily with a placebo MDI. Patients kept daily records and had clinical evaluations at regular intervals for 24 weeks. Seventy-six percent of the patients completed the study.

The strict inclusion criteria in this study assured that the study population consisted of patients meeting criteria for moderate or severe persistent asthma—those patients most likely to benefit from asthma controller therapy. Reasonable attempts were made to blind patients to treatment, but more patients in the fluticasone group reported hoarseness and oral pharyngeal candidiasis, possibly

allowing them and the researchers to intuit their treatment assignment.

■ **OUTCOMES MEASURED** The primary outcome was percent change in FEV₁. Other outcomes included peak flow rate, symptom-free days, daily albuterol use, asthma symptom scores, asthma quality-of-life scores, and patient-rated satisfaction with treatment. Safety was also assessed by reports of clinical adverse events and number of asthma exacerbations.

■ **RESULTS** Using an intent-to-treat analysis, the fluticasone group had a significantly greater sustained change in FEV₁ (22% vs 14%; $P < .001$). Significant differences were noted after just 2 weeks of treatment. Significant differences favoring fluticasone were also found in all secondary outcomes including the patient-oriented outcomes of change in asthma symptom scores (-0.91 vs -0.57 ; $P < .001$), asthma quality-of-life scores (1.3 vs 1.0; $P = .004$), and patient-rated satisfaction with treatment (83% of fluticasone patients satisfied vs 66% of montelukast patients satisfied; $P < .001$). No differences were noted in overall incidence of adverse events between treatment groups, but significantly more fluticasone-treated patients reported hoarseness (9 vs 0; $P = .002$) and oral pharyngeal candidiasis (8 vs 0; $P = .008$). The incidence of asthma exacerbations was similar (19 fluticasone-treated patients vs 21 montelukast-treated patients).

RECOMMENDATIONS FOR CLINICAL PRACTICE

This study confirms earlier studies indicating that inhaled steroids should be first-line treatment for moderate-to-severe persistent asthma. When compared with montelukast, inhaled fluticasone showed greater improvements in clinical measures of asthma, as well as patient-oriented measures such as symptom scores, quality-of-life scores, and patient-rated satisfaction. However, moderate-to-severe persistent asthma appears to require more therapeutic measures than just low-dose fluticasone. Despite treatment, patients still used albuterol on more than half of the days, only one third of days were symptom-free, and symptom scores improved by less than 1 point on a 6-point scale.

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Azithromycin no more effective than vitamin C for acute bronchitis

Evans AT, Husain S, Durairaj L, et al. Azithromycin for acute bronchitis: a randomised, double-blind, controlled trial. *Lancet* 2002; 359:1648–54.

■ **BACKGROUND** The results of studies evaluating the effectiveness of antibiotic treatment for acute bronchitis are conflicting, some with uncertain reliability and validity. Although most studies of antibiotics have focused on cure of disease or reduction in symptoms, this study tested whether patients with acute bronchitis who were treated with azithromycin experienced greater improvements in health-related quality of life than those treated with vitamin C. The authors chose to compare azithromycin with vitamin C instead of traditional placebo because they believed potential patients might refuse to participate in the study if there was a chance they would receive a placebo. Evidence has shown that vitamin C at the doses used in this study is ineffective in the treatment of acute bronchitis or other respiratory illnesses, making the vitamin a reasonable placebo for this study.¹

■ **POPULATION STUDIED** The authors studied 220 adults with cough lasting 2–14 days who were diagnosed with acute bronchitis after presenting to an ambulatory screening clinic in Chicago, Illinois. Patients were excluded if they had any underlying lung disorder, clinical characteristics of pneumonia, antibiotic treatment within the previous 2 weeks, pregnancy, steroid treatment, or had been started on an angiotensin-converting enzyme inhibitor within the previous 4 weeks.

■ **STUDY DESIGN AND VALIDITY** This study was a randomized, double-blinded, controlled trial with concealed allocation. Patients were randomized to receive a total of 1.5 g of either azithromycin or vitamin C over 5 days (500 mg on the first day, then 250 mg/day for 4 more days). All patients also received symptomatic care with dextromethorphan and an albuterol inhaler with a spacer. Trained research assistants interviewed patients on enrollment in the study to assess their baseline health-related quality of life. The interview, consisting of 22 questions adapted from similar instruments developed at McMaster University, was repeated on days 3 and 7. For each of the questions, patients were asked to rate how troubled they had been during the previous few days as a result of their bronchitis symptoms on a 7-point scale. Follow-up was for 7 days from the beginning of the study and was 85.9% com-

plete. Analysis was by intention to treat.

This well-done study assessed the adequacy of blinding by asking all patients to guess whether they received azithromycin or vitamin C (guessing results were similar in both groups and were no better than chance). Although the initial plan for the study was to enroll 400 patients, the researchers ended the trial early due to the precision of the findings. The sample size of 220 provided a power of 95%–99% to detect a difference of 0.5 points in health-related quality of life (determined to be the minimum clinically important difference based on published research of similar scales). The small size of the study limited the researchers' ability to do subgroup analysis.

■ **OUTCOMES MEASURED** The primary outcome measured was health-related quality of life on day 7 of follow-up. Secondary end points were return to usual daily activities at follow-up and adverse effects.

■ **RESULTS** The adjusted difference in health-related quality of life between the patients taking azithromycin and those taking vitamin C was not significant on day 7 of the study (difference = 0.03; 95% confidence interval [CI], –0.20 to 0.26). Overall, 89% of patients in both groups returned to work by day 7 (difference = 0.5%; 95% CI, –10% to 9%). No difference was noted in the treatment of acute bronchitis in otherwise healthy adults.

RECOMMENDATIONS FOR CLINICAL PRACTICE

Azithromycin is no more effective than vitamin C in treating acute bronchitis in healthy adults. Given the evidence that treatment with vitamin C is not effective in respiratory illnesses, azithromycin appears equally ineffective. With increasing health care costs and rising concerns about antibiotic resistance, azithromycin, and probably other antibiotics, should not be used to treat acute bronchitis in otherwise healthy adults.

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Acarbose delays onset of type 2 diabetes mellitus

Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002; 359:2072-7.

■ **BACKGROUND** Patients who develop type 2 diabetes initially pass through a state of impaired glucose tolerance. Therapies that reduce resistance to insulin or protect β cells could prevent or delay the progression to diabetes.

■ **POPULATION STUDIED** This multinational study was conducted in Canada, Israel, and Western Europe. Investigators recruited high-risk patients through newspaper advertising. They screened 14,742 individuals with a body mass index (BMI) between 25 and 40 kg/m² (mean 31.0 kg/m²) with a 2-hour glucose tolerance test. Eligible subjects had impaired glucose tolerance, defined as a 2-hour plasma glucose concentration of ≥ 140 mg/dL (7.8 mmol/L) and < 200 mg/dL (11.1 mmol/L). Investigators excluded subjects who had a serum creatinine concentration ≥ 1.5 mg/dL, or who had taken thiazide diuretics, β -blockers or nicotinic acid within the past 3 months.¹ Ninety-seven percent of the 1429 randomized patients were white and 48% were men. The average age was 54.3 years.

■ **STUDY DESIGN AND VALIDITY** This was a randomized, double-blind, placebo-controlled trial. Randomization was done at each center in a sequential manner in blocks of 4 and 6 patients, using a centrally generated random allocation sequence and numbered drug containers. Allocation was appropriately concealed. Treatment groups were comparable at baseline. To minimize gastrointestinal side effects, patients randomized to acarbose were started at 50 mg/day and gradually increased to a maximum of 100 mg 3 times a day with meals or to the maximum tolerated dose. The mean daily dose was 197 mg. All patients met with a dietitian before randomization and then yearly, were instructed in a weight reduction or maintenance program, and were encouraged to exercise. Patients saw a nurse every 3 months for a pill count and fasting plasma glucose measurement. Patients with abnormal fasting plasma glucose levels had a 2-hour oral glucose tolerance test, and all patients had a yearly glucose tolerance test. Patients were followed for a mean of 3.3 years. Ninety-six percent of patients were accounted for at the end of the trial. All patients at the end of the trial who were not diagnosed with diabetes were placed on placebo and followed for an additional 3 months. An intention-to-treat analysis was performed using appropriate statistical methods.

This well-done trial had no threats to internal

validity. The homogeneity of the study population could limit generalizability, as ethnic groups more frequently encountered in the United States, for example African Americans or Hispanic Americans, might have dietary habits that could affect the tolerability, and thus the effectiveness, of acarbose.

■ **OUTCOMES MEASURED** The primary outcome measured was time to development of type 2 diabetes, defined by a plasma glucose concentration of > 200 mg/dL (11.1 mmol/L) after a 2-hour glucose tolerance test.

■ **RESULT** Patients treated with acarbose were less likely to develop type 2 diabetes after 3.3 years (17% vs 26%, numbers needed to treat = 11, $P = .0003$). The effectiveness of acarbose became apparent at 1 year. More patients taking acarbose dropped out of the trial secondary to gastrointestinal side effects (31% vs 18%, numbers needed to harm = 8, $P < .0001$). When acarbose was stopped at the end of the study period, more patients who had been treated with acarbose developed diabetes in the next 3 months than did patients who were treated with placebo (15% vs 11%).

RECOMMENDATIONS FOR CLINICAL PRACTICE

Treating patients with impaired glucose tolerance with acarbose will delay the onset of type 2 diabetes for at least 3.3 years. It is unclear whether acarbose actually prevents diabetes or just delays its onset, and whether acarbose reduces morbidity or mortality secondary to diabetes. One third of patients who take acarbose will not tolerate the medication, which must probably be continued indefinitely to remain effective. Lifestyle modification, including dietary changes and regular moderate physical activity, should be the first-line therapy to prevent diabetes in patients with impaired glucose tolerance.² Acarbose can be used for patients who are not willing or able to change behavior.

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Epidurals do not increase the incidence of cesarean delivery

Leighton BL, Halpern SH. The effects of epidural analgesia on labor, maternal, and neonatal outcomes: a systematic review. *Am J Obstet Gynecol* 2002; 186(suppl):S69-77.

■ **BACKGROUND** Epidural analgesia effectively relieves labor pain, but questions persist about possible adverse effects of epidurals on labor, the mother, and the neonate. This meta-analysis compared the impact of epidural analgesia with parenteral opioids on birth outcomes.

■ **POPULATION STUDIED** A total of 4721 women from 16 studies were identified. The participants were nulliparous and multiparous women with uneventful pregnancies undergoing spontaneous and induced labor. Thus, the subjects are likely to be similar to those seen by many family physicians, although more detail about race, gestational age, and other obstetric risk factors would have been useful.

■ **STUDY DESIGN AND VALIDITY** The authors searched MEDLINE, EMBASE, the Cochrane Library, and meeting abstracts and references of review articles for randomized controlled trials comparing epidural analgesia with parenteral opioids during labor. Prospective cohorts were used only if no randomized controlled trial was available for a particular outcome and articles met criteria for quality. The authors assessed methodological quality with the Jadad scale. Heterogeneity was assessed with a chi-square test; Cochrane software was used to combine the results using a random effects model on an intent-to-treat basis.

The methodology of this overview was strong. Its strengths included thoroughness of the literature search, attention to many outcomes, and homogeneity of available studies. Weaknesses were relatively minor and included unblinded review of studies, inattention to concealment of randomization, and inattention to potential confounding issues such as epidural technique, social support, and other aspects of obstetric management. Clinicians should keep in mind that patient enrollment in this kind of trial is difficult—potentially biasing results—and that this study did not include comparisons of patients receiving epidural agents with patients who chose nonpharmacologic methods of pain control.

■ **OUTCOMES MEASURED** Maternal outcomes included maternal pain; satisfaction with pain control; labor duration; oxytocin use; temperature of $>38^{\circ}\text{C}$; incidence of cesarean and instrumental delivery, and incidence of postpartum urinary incontinence and low back pain. Neonatal outcomes included 1- and 5-minute Apgar scores,

fetal heart rate abnormalities, umbilical artery pH, and lactation success. Spinal headaches, neonatal jaundice, and hypoglycemia as well as treatment costs were not addressed.

■ **RESULTS** Available trials were of low to moderate quality, with none having blinded assessment of outcomes. The rate of cesarean delivery was similar for patients receiving epidural and parenteral opioid analgesia; analyzing only higher quality trials did not change this result. Compared with women receiving parenteral opioids, patients receiving epidural analgesia had significantly lower pain scores (mean weighted difference = -40 on 100-mm scale; 95% confidence interval [CI], -42 to -38) and greater satisfaction with pain relief (odds ratio [OR] = 0.27; 95% CI, 0.19–0.38; number needed to treat [NNT] = 5). Women receiving epidural analgesia also had a 15-minute longer second stage and more oxytocin use (OR = 2.80; 95% CI, 1.89–4.16; NNT = 5), fever (OR = 5.6; 95% CI, 4.0–7.8; NNT = 5), and instrumental delivery (18.9% vs 12.2%; OR = 2.08; 95% CI, 1.48–2.93; NNT = 14). The rate of instrument use for shoulder dystocia was similar. For patients given parenteral opioid analgesics, naloxone was used most frequently. No differences were noted in incidence of low umbilical pH, low 5-minute Apgar scores, or fetal heart rate abnormalities. Randomized controlled trials were unavailable for lactation and incontinence outcomes; 1 prospective cohort study for each outcome found no differences.

RECOMMENDATIONS FOR CLINICAL PRACTICE

Epidural analgesia provides better pain control than parenteral opioids without increasing cesarean delivery rates. Clinicians should counsel women choosing epidural agents, however, to expect a small increase in second-stage labor and a higher rate of maternal fever, use of oxytocin, and instrumented delivery. Clinicians should keep in mind that this study did not compare epidural analgesia with nonpharmacologic interventions, such as social support, which are known to have potent influence on labor course. Further studies of the impact of analgesia choice on breast-feeding and maternal incontinence are important.

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Cost effectiveness of aspirin vs clopidogrel for secondary prevention of coronary heart disease

Gaspoz JM, Coxson PG, Goldman PA, et al. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. *N Engl J Med* 2002; 346:1800-6.

■ **BACKGROUND** Clopidogrel is a platelet aggregation inhibitor that is slightly more effective than aspirin in reducing the risk of cardiovascular events in individuals with preexisting cardiovascular disease (0.51% annual absolute risk reduction; *Lancet* 1996; 348:1329-39). However, clopidogrel is currently 80 times more expensive than aspirin. The authors looked at the risks, benefits, and costs of long-term use of various therapeutic strategies involving these 2 medications.

■ **POPULATION STUDIED** A computer simulation, known as the Coronary Heart Disease Policy Model, was used to predict the number of patients in the United States (35-84 years) who would develop coronary disease before or during the next 25 years, as well as the number of subsequent cardiovascular events and deaths these individuals would experience. Only patients predicted to survive their first month after a cardiac event were included in the therapeutic intervention analysis. Parameters for the model were based on cohort studies and clinical trials found in the medical literature.

■ **STUDY DESIGN AND VALIDITY** Beginning with their estimated number of Americans with coronary disease and cardiovascular events, the authors predicted the reduction in events using aspirin, clopidogrel, or both. The 4 possible treatment strategies were (1) aspirin 325 mg/day for all eligible patients; (2) aspirin for all eligible patients or clopidogrel 75 mg/day for the remaining 5.7% ineligible for aspirin; (3) clopidogrel 75 mg/day for all patients plus aspirin for all eligible patients. They also considered costs of various interventions, including hospitalizations, rehabilitation services, outpatient and home services, and treatment for adverse drug effects such as gastrointestinal bleeding. To carry out the cost-effectiveness analysis over such a long time period, the authors discounted costs at a rate of 3% per year (a typical amount) and converted all values to year-2000 US dollars. Sensitivity analysis used upper and lower bounds of reductions from past trial data to give a reasonable range of values. As with all hypothetical cost-effectiveness studies, this study only represents the authors' best esti-

mates of costs and benefits, not actual results from a therapeutic trial or cohort. Issues such as the safety of combination therapy over this prolonged time period have not been well established.

■ **OUTCOMES MEASURED** The main outcome was the cost per quality-adjusted life year (QALY) gained, that is, the cost of an additional year of optimal health.

■ **RESULTS** Aspirin alone in all eligible patients (strategy #1) resulted in an estimated \$11,000 per QALY gained. Giving clopidogrel to the 5.7% of patients ineligible for aspirin (strategy #2) would prevent some subsequent events at an increased cost, resulting in a total estimate of \$31,000 per QALY gained compared with the first strategy. Using clopidogrel alone for everyone (strategy #3) led to a very high estimated cost of \$250,000 per QALY gained compared with strategy #2. Combination therapy of clopidogrel for everyone plus aspirin for the 96.3% of eligible patients (strategy #4) resulted in an estimated cost of \$130,000 per QALY gained compared with strategy #2. However, in patients with annual risks 3 times as high as that of the average patient with coronary disease, this ratio fell below \$64,000 per QALY gained.

A cost of \$50,000 per QALY gained is generally considered acceptable in Western society, and as such strategy #2 appears to balance cost and benefits most reasonably. Because the cost of clopidogrel will probably decrease over the coming years, the authors also took this price change into account for various strategies. If the cost of clopidogrel fell 70% (to approximately \$1.00 per dose), then strategy #4 (combination therapy) would drop below the \$50,000 threshold.

RECOMMENDATIONS FOR CLINICAL PRACTICE

Considered from a societal standpoint, clopidogrel at its current price has acceptable cost effectiveness when used by patients with cardiovascular disease who cannot take aspirin. If the cost of clopidogrel falls substantially in the future, combination therapy with both clopidogrel and aspirin in these patients may also be a reasonable public health policy.

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Inhaled salmeterol prevents high-altitude pulmonary edema

Sartori C, Allemann Y, Duplain H, et al. Salmeterol for the prevention of high-altitude pulmonary edema. *N Engl J Med* 2002; 346:1631–6.

■ **BACKGROUND** High-altitude pulmonary edema (HAPE) is a life-threatening manifestation of high-altitude illness. Although conventional medications such as acetazolamide and dexamethasone can prevent acute mountain sickness (a more common and less severe stage of high-altitude illness). Dexamethasone is known to be ineffective and acetazolamide has not been studied specifically for HAPE.¹ Beta-agonists may decrease HAPE by promoting the clearance of alveolar fluid and thus relieving pulmonary edema and alveolar hypoxia. This study investigated the use of salmeterol to prevent HAPE in climbers at high risk for this condition.

■ **POPULATION STUDIED** The investigators studied 37 mountaineers who had a history of HAPE (average of 2 previous episodes per subject). Most subjects were men, and the average age was 48 years. Baseline demographics were similar between groups. The population was appropriate for the condition being studied, although these men were at much higher risk for HAPE than the average recreational mountain climber.

■ **STUDY DESIGN AND VALIDITY** This study was double-blind, randomized, and placebo controlled. Starting the day before ascent, the climbers inhaled either salmeterol 125 µg (about 3 times the normal asthma dosage) or placebo every 12 hours via metered-dose inhaler with spacer. They ascended (via cable car and mountaineering) from 1130 m to a high-altitude (4559 m) research laboratory in Italy over a period of 22 hours. Investigators then observed the subjects over a period of 2 days and nights for clinical and laboratory signs of HAPE and acute mountain sickness. Participants who developed symptoms of HAPE were evacuated to low altitude.

The results of this study may not apply to climbers who are at low risk of HAPE or persons who ascend at a slower pace. There are also some limitations to the design. Although the abstract stated that this study was a double-blind, randomized trial, the text did not describe how blinding or randomization was accomplished. Allocation concealment also was not described but is unlikely to be an issue in this study

because of the small sample size. All 37 patients were included in the data analysis.

■ **OUTCOMES MEASURED** The major patient-oriented end point was clinical and radiographic evidence of pulmonary edema. Investigators recorded Lake Louise Acute Mountain Sickness scores, arterial oxygen saturations, and carbon dioxide and oxygen arterial partial pressures. They also compared chest radiographs obtained at the high-altitude laboratory.

■ **RESULTS** The incidence of pulmonary edema was less in the salmeterol group than with placebo (74% vs 33%; $P = .02$; numbers needed to treat = 2.5). Lake Louise Acute Mountain Sickness scores were significantly better in the salmeterol group than in the placebo group (5.8 vs 11.5 out of a possible 24; $P < .001$). Chest radiographs, arterial oxygen saturations, and oxygen arterial partial pressures were also significantly improved with salmeterol.

RECOMMENDATIONS FOR CLINICAL PRACTICE

Inhaled salmeterol decreases the incidence of HAPE in climbers with previous episodes of this condition. Nifedipine is the only other drug specifically shown to prevent HAPE²; although both the nifedipine study and the current salmeterol study were small, the 2 drugs appear roughly comparable in efficacy. It is unclear whether salmeterol would be effective for preventing more common and less severe stages of high-altitude illness (eg, acute mountain sickness), or whether the drug would be worthwhile in persons without a history of HAPE. Because of established efficacy in preventing acute mountain sickness, acetazolamide or dexamethasone should remain first-line agents for prevention of high-altitude illness in most climbers, with salmeterol or nifedipine added for individuals at high risk of HAPE.

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Vasectomy not a risk factor for prostate cancer

Cox B, Sneyd MJ, Paul C, Delahunt B, Skegg DCG. Vasectomy and the risk of prostate cancer. *JAMA* 2002; 287:3110-5.

■ **BACKGROUND** Several case-control and cohort studies since the early 1990s have shown conflicting results on a possible association between vasectomy and prostate cancer risk. A recent systematic review failed to show a causal association and suggested several possible mechanisms for inconclusive results. This study addressed some of these limitations.

■ **POPULATION STUDIED** The study included 923 men in New Zealand between the ages of 40 and 74 years with newly diagnosed prostate cancer (cases). All men were on the general electoral roll and had a history of marriage. The control group was randomly selected from the general electoral roll ($n = 1224$), and frequency matching to cases was performed in 5-year age groups. The mean age for cases and controls was 66.3 and 65.1 years, respectively. All cases and controls had telephone numbers for data collection purposes. Because nearly all study subjects were of European descent (97%), the results may not apply to other ethnic groups.

■ **STUDY DESIGN AND VALIDITY** This national, population-based, case-control study was performed on all newly diagnosed cases of prostate cancer during a specified time (April 1, 1996, to December 31, 1998). Controls were randomly selected from the general electoral roll in which about 95% of adults are listed. Of potential cases and controls, only 12% and 20%, respectively, could not be contacted due to death, doctor or subject refusal, severe illness, inability to trace, or language difficulties.

Data on cases and controls were collected using interviewers who were initially blind to whether they were contacting a case or a control subject. Information regarding previous illnesses, smoking and alcohol consumption, prostate-specific antigen testing, digital rectal examination, previous urological symptoms and operations, family history of cancer, sociodemographic characteristics, and vasectomy was collected. The study hypothesis was not revealed to the patients being interviewed.

Due to the high prevalence of vasectomies in New Zealand (reportedly the highest in the world)

and the large number of cases and controls, the study had 99% statistical power to detect a relative risk of 1.5 or higher at a 5% significance level. Even after 25 years since vasectomy, the study had 80% statistical power to detect the same risk.

To assess the possibility of recall bias for a history of vasectomy (ie, men with prostate cancer would be more likely to remember that they had a vasectomy than men without cancer), the authors attempted to obtain the records of a random sample of 103 men. Only 49 records were obtained during the study time period, but all self-reports were confirmed. Although recall is a potential source for error, it would seem unlikely that many men would have doubts about having undergone a vasectomy. Other possible sources of bias including interviewer bias and detection bias (due to close surveillance by a urologist) were adequately addressed in the study.

■ **OUTCOMES MEASURED** The primary outcome measured was the relative risk (RR) of prostate cancer for men who had vasectomies compared with that for men who had not undergone the procedure.

■ **RESULTS** No association between prostate cancer and vasectomy was found (RR = 0.92; 95% confidence interval [CI], 0.75-1.14). Even after 25 years since vasectomy, no association was found (RR = 0.92; 95% CI, 0.68-1.23). Adjustments were made for social class, geographic region, religious affiliation, and family history of prostate cancer without any effect on the risk.

RECOMMENDATIONS FOR CLINICAL PRACTICE

This study found that having a vasectomy does not increase a man's risk of developing prostate cancer, even after 25 or more years of follow-up. Because a previous systematic review also showed no conclusive evidence for an increased risk of prostate cancer after vasectomy, practitioners can confidently advise patients requesting vasectomies of the safety advantages compared with other methods of sterilization.

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