



## In patients with diabetes and hypertension, should treatment start with an ACE inhibitor instead of a diuretic or beta blocker?

Niskanen L, Hedner T, Hansson L, Lanke J, Niklason A. Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic  $\beta$ -blocker-based treatment regimen. A subanalysis of the captopril prevention project. *Diabetes Care* 2001; 24:2091-6.

- **BACKGROUND** About half of all patients with type 2 diabetes will eventually die because of a cardiovascular disease-related event. This study compared whether captopril was better than other beta blockers or diuretics at decreasing cardiovascular morbidity and mortality in the patient with diabetic hypertension.
- **POPULATION STUDIED** Patients were 572 diabetics enrolled in the larger captopril prevention project (*Lancet* 1999; 353:611-6), a study of 10,985 hypertensive patients from 536 health centers in Sweden and Finland. Subjects were male and female, aged 25 to 66 years, with primary hypertension (untreated and treated) and untreated diastolic blood pressure of at least 100 mm Hg on 2 occasions. Factors for exclusion: secondary hypertension, elevated serum creatinine levels, or conditions requiring beta blocker therapy.
- **STUDY DESIGN AND VALIDITY** This research was a randomized controlled trial. Neither patients nor physicians were blinded, although endpoints were assessed by a committee blinded to treatment assignment. Initial allocation to treatment group was concealed from enrolling physicians. Patients were initially randomized to receive blood pressure treatment with either captopril (up to 100 mg per day) or conventional treatment with a diuretic agent or beta blocker. Patients not achieving blood pressure control were treated at the discretion of the physician with a diuretic in the captopril group or with a combination of beta blocker and diuretic in the conventional group. A calcium channel blocker could be added as a third step in either group. The goal of therapy was diastolic blood pressure less than 90 mm Hg. Patients were evaluated for an average of 6.1 years.

This study was well done. Although patients and physicians were not masked to therapy, assessors of outcomes were masked. The design allowed for the physicians to decide the next course of treatment, as in typical practice. The goal blood pressure in this study was higher than 130/85 mm Hg, as recommended by JNC VI, and higher than 130/80 mm Hg, as recommended by the American Diabetes Association. Future reductions in outcomes in both groups might have been seen with these lower blood pressures.

■ **OUTCOMES MEASURED** The primary outcome measured was fatal and nonfatal myocardial infarction (MI) and stroke as well as other cardiovascular deaths in patients with diabetes. Other outcomes measured were the development of other cardiac disorders and noncardiovascular effects.

■ **RESULTS** The primary outcome of fatal and nonfatal MI and stroke, as well as that of other cardiovascular deaths, was significantly lower in the captopril-treated group than in the conventional treatment group (RR = 0.59, 95% CI 0.38-0.91, number needed to treat [NNT] = 16). Overall mortality was lower as well (RR = 0.54, 95% CI 0.31-0.95). Individually, the rates of stroke, fatal cardiovascular events, and overall mortality did not differ between the 2 groups. MI (fatal and nonfatal) was markedly less frequent in the captopril group (RR = 0.34, 95% CI 0.17-0.67, NNT = 16).

### RECOMMENDATIONS FOR CLINICAL PRACTICE

Captopril may be the initial agent of choice for hypertension in diabetic hypertensive patients, especially those with poor glycemic or lipid control. Captopril was shown to reduce overall mortality, MI risk, and overall cardiac events significantly better than did treatment initiated with either a diuretic agent or a beta blocker.

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## Does cerclage prevent preterm birth or decrease perinatal morbidity when performed on the identification of a short cervix by second-trimester ultrasound?

Rust OA, Atlas RO, Reed J, van Gaalen J, Balducci J. Revisiting the short cervix detected by transvaginal ultrasound in the second semester: why cerclage therapy may not help. *Am J Obstet Gynecol* 2001; 185:1098-105.

■ **BACKGROUND** Because strong evidence supports the association between cervical length and preterm delivery and perinatal morbidity, transvaginal ultrasound (TVUS) has been used to identify patients with premature cervical change who may benefit from therapeutic cerclage placement. Observational studies report conflicting results regarding the benefits of therapeutic cerclage. Few randomized trials regarding the efficacy of cerclage therapy have been reported.

■ **POPULATION STUDIED** This study enrolled 113 women from an urban outpatient perinatal testing center that had cervical changes identified by TVUS during the second trimester of pregnancy. Specific changes were dilation of the internal os and either (1) prolapse of membranes of at least 25% of the total cervical length or (2) a distal cervical length of less than 2.5 cm. Subjects were excluded if they had membrane prolapse beyond the external os or any other contraindication to cerclage. All participants were similar with regard to age, risk factors for preterm labor, and history of preterm deliveries. However, patients in the no-cerclage group tended to have an increased rate of second-trimester deliveries (12.1 vs 27.3,  $P = .07$ ).

■ **STUDY DESIGN AND VALIDITY** This was an open randomized controlled trial. Participants with cervical changes were randomized to receive either McDonald cerclage ( $n = 55$ ) or no cerclage ( $n = 58$ ). Before randomization, all patients received amniocentesis, multiple urogenital cultures, indomethacin, and clindamycin. All subjects were treated identically (including serial ultrasonography and modified bed rest) after the intervention. Routine prenatal care continued and cerclage was removed at 36 weeks' gestational age or for any of the following reasons: rupture of membranes, preterm labor refractory to tocolytic therapy, or other indication for delivery. Analysis was done by intention to treat. The authors developed a stepwise logistic regression model to analyze dependent and independent variables. It is uncertain whether allocation assignment to treatment group was concealed.

The study population is generalizable and large enough to have adequate power to support a negative result. Despite reporting good data that cerclage is not beneficial in preventing preterm deliveries and decreasing neonatal morbidity, the authors wanted to identify several risk factors that were associated with

failure of the cerclage. The logistic regression model, although statistically sound, makes this study difficult to follow and the results do not add important clinical information. In addition, not all the significant data are clearly given, specifically the data regarding perinatal morbidity between the 2 groups.

■ **OUTCOMES MEASURED** The primary outcomes measured were gestational age at delivery and neonatal morbidity, defined as none, minimal, severe, or death. The authors analyzed a number of other variables to determine any associations with the primary outcomes but did not address cost effectiveness or patient satisfaction.

■ **RESULTS** There were no statistical differences in the primary outcomes of gestational age at delivery of less than 34 weeks' gestation (34.9 vs 36.2,  $P = .8$ ) or perinatal morbidity, reported only as perinatal death (12.7 vs 11.9,  $P = .9$ ). The regression model analysis identified preterm labor, chorioamnionitis, and abruption as significant risk factors associated with the primary outcomes.

### RECOMMENDATIONS FOR CLINICAL PRACTICE

In the current study, therapeutic cerclage did not benefit patients identified as having a short cervix by second-trimester ultrasound. These findings do not support the routine use of second-trimester ultrasound to screen for premature cervical changes. Risk factor analysis provided further data showing that preterm deliveries are a multifactorial process and that patients with preterm labor, infection, and abruption do not benefit from cerclage.

Another well-designed but smaller randomized controlled trial<sup>1</sup> studied a subset population of pregnant women at high risk for cervical incompetence and found therapeutic cerclage to be beneficial. Comparison of these 2 studies suggests that a subset population might benefit from cerclage therapy. Unfortunately, with current medical diagnostics, this ideal patient is not easily identifiable. An ongoing Cochrane Review that addresses cerclage efficacy may help clarify these discrepancies.

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### REFERENCE

1. Althuisius SM, Dekker GA, Hummel P, Bekedam DJ, van Geijn HP. Final results of the Cervical Incompetence Prevention Randomized Cerclage Trial (CIPRACT): therapeutic cerclage with bedrest versus bedrest alone. *Am J Obstet Gynecol* 2001; 185:1106-12.

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## Which is better for the management of postpartum perineal pain: ibuprofen or acetaminophen with codeine?

Porter EA, Janssen PA, Grange CS, Douglas MJ. Ibuprofen versus acetaminophen with codeine for the relief of perineal pain after childbirth: a randomized controlled trial. *CMAJ* 2001; 165:1203-9.

■ **BACKGROUND** Pain that occurs from perineal laceration or episiotomy during childbirth can be severe and is often undertreated. This randomized double-blind controlled trial was designed to compare the effectiveness and side effects related to 2 common analgesics used in this setting: ibuprofen and acetaminophen with codeine.

■ **POPULATION STUDIED** The study looked at 237 women who delivered vaginally and who had either a third- or fourth-degree perineal laceration or an episiotomy. The trial took place between August 1995 and November 1996 at a tertiary-care teaching and referral center for obstetric care in Vancouver, BC, Canada. Approximately 35% of the women enrolled spoke Cantonese or Mandarin; these women were supplied with consent forms in Chinese script translated by a bilingual nurse. Women were excluded for allergy to either of the study drugs, history of drug dependence, regular use of analgesic drugs, or any medical condition known to be potentially exacerbated by opioids or nonsteroidal anti-inflammatory drugs. Women were also excluded if any major postpartum complication, including postpartum hemorrhage, had occurred. The 2 groups of women did not differ significantly in sociodemographic characteristics or in gravidity and parity. All but 4 of the 237 women enrolled completed the study. The 2 treatment groups did not differ significantly except that the ibuprofen group contained more women who had had forceps delivery.

■ **STUDY DESIGN AND VALIDITY** This study was a randomized, double-blind trial with no placebo control. Randomization was done in blocks of 20 and stratified on the use of forceps, which were postulated to contribute significantly to postpartum pain. Women were randomized within 1 hour after delivery to receive either 400 mg ibuprofen or 600 mg acetaminophen with 60 mg codeine and 30 mg caffeine every 4 hours for 24 hours after birth. The pharmacy allocated the patients to the treatment groups. Women and their nurses were blinded. Women who did not request analgesia were not enrolled.

■ **OUTCOMES MEASURED** The primary outcome measured was severity of pain rated on a 10-cm visual analog scale. Other outcomes evaluated were the number of doses of medication, dosing intervals, treatment failures, side effects, overall level of satisfaction, cost of treatment, and nursing time required for medication administration.

■ **RESULTS** Both groups had similar pain ratings before taking the first dose of analgesic (rating of 3.4 for ibuprofen vs 3.3 for acetaminophen plus codeine plus caffeine) as well as number of medication doses in 24 hours (3.4 vs 3.3) and treatment failures (13.8% vs 16%). Among treatment failures, 78% occurred in women who had had forceps delivery. Subjects receiving ibuprofen experienced fewer side effects (52.4% vs 71.7%,  $P = .006$ , number needed to harm = 5.2). Overall satisfaction between the groups did not differ. Ibuprofen (\$0.02/tablet) was less expensive than acetaminophen with codeine (\$0.05/tablet). Because of the need for additional inventory control, the administration of each dose of the codeine combination took an average of 10 minutes, more time than the administration of ibuprofen.

### RECOMMENDATIONS FOR CLINICAL PRACTICE

Ibuprofen and acetaminophen with codeine were similarly effective for the management of postpartum perineal pain caused by significant maternal trauma. Women with forceps-assisted deliveries had significantly more pain and were more likely to fail treatment with either medication. Patients receiving acetaminophen with codeine experienced more side effects, most notably nausea, stomach pain, and disorientation. Ibuprofen should be used as a standard first-line medication for the treatment of perineal pain in this setting. It is less expensive, can be self-administered by patients from the bedside, and has fewer side effects while maintaining the same effectiveness for analgesia. Acetaminophen with codeine should be reserved for women who do not tolerate ibuprofen.

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## Should antioxidants be added to simvastatin and niacin for patients with coronary disease?

Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001; 345:1583-92.

■ **BACKGROUND** Antioxidant vitamins are commonly used in patients with coronary disease, but benefits have not been demonstrated. This randomized controlled trial studied whether addition of antioxidants to a simvastatin–niacin regimen improved outcomes.

■ **POPULATION STUDIED** The investigators enrolled 160 patients with known coronary disease from the Seattle area and Canada. Subjects were included if they had clinical coronary disease (previous myocardial infarction [MI], coronary interventions, or confirmed angina); 3 or more coronary arteries with more than 30% stenosis or 1 stenosis more than 50%; high-density lipoprotein (HDL) cholesterol levels less than 35 mg/dL in men or 40 mg/dL in women; low-density lipoprotein (LDL) cholesterol levels less than 145 mg/dL; and triglyceride levels less than 400 mg/dL.

Patients were excluded if they had a history of coronary artery bypass surgery, severe hypertension, gout, uncontrolled diabetes, or liver, thyroid, or kidney disease. Patients' average age was 53 years; 13% were female. No information about race or ethnicity was provided. More than half of the patients (55%) had a prior MI; 49% had previous angioplasty; 16% had diabetes; and 24% were current smokers. Thus, the patients were similar to high-risk patients seen by family physicians for secondary prevention, although caution should be exercised in extrapolating results to women and nonwhites.

■ **STUDY DESIGN AND VALIDITY** This was a double-blinded, placebo-controlled trial. Patients were randomly assigned to 1 of 4 regimens: simvastatin–niacin, antioxidant vitamins, simvastatin–niacin plus antioxidants, or placebo. Patients receiving simvastatin had their dose titrated to a goal LDL level of 40 to 90 mg/dL (mean final dose 13 mg/day). In patients receiving niacin, the dose was titrated over 1 month to at least 1000 mg twice per day (mean final dose 2.4 grams/day). Niacin 50 mg twice per day was used as the placebo to produce a flushing effect and thus keep patients blinded. Antioxidants were given twice daily, with total dosage of 800 IU vitamin E, 1000 mg vitamin C, 25 mg natural beta carotene, and 100 µg selenium. Coronary angiography was performed at baseline and finish; comparison of films was blinded. Patients were followed over 3 years. Analysis was by intent to treat with control for confounding with Cox proportional hazards.

The methodology was excellent. Strengths include the randomized design with concealed allocation, excellent follow-up (99.4%), and assessment of both angiographic and clinical outcomes. Weaknesses were minor and include the lack of rigorous review of clinical outcomes, the lack of power in the comparison of the antioxidants alone with placebo, and inattention to aspirin use, which may have been greater in patients taking niacin.

■ **OUTCOMES MEASURED** The primary clinical endpoint was the occurrence of a cardiovascular event: revascularization, nonfatal MI, or death from coronary causes. The angiographic primary endpoint was the change in stenosis of the most severe lesion in the 9 proximal coronary segments. Cost, quality of life, and patient satisfaction were not addressed.

■ **RESULTS** The groups were similar at baseline, with the exception that diabetics were more prevalent in the group receiving simvastatin–niacin plus antioxidants and less prevalent in the simvastatin–niacin alone group ( $P = .04$ ). Patients receiving simvastatin–niacin had significantly fewer cardiovascular events than those given placebo (21% vs 2.6%,  $P = .003$ , number needed to treat = 4.7). Addition of antioxidants actually blunted this effect: when antioxidant therapy was added to lipid lowering, the rate of clinical events increased to that observed with placebo. There was also no difference between patients receiving antioxidants alone and those receiving placebo. These clinical results were mirrored by the angiographic data: patients receiving simvastatin and niacin experienced a reduction in average coronary stenosis ( $P < .001$ ), whereas all other groups showed an increase in stenosis ( $P < .005$ ).

### RECOMMENDATIONS FOR CLINICAL PRACTICE

This well-designed study provides strong evidence that antioxidants should not be used in patients with preexisting coronary disease, either alone or in addition to simvastatin and niacin. The combination of a statin and niacin reduced adverse cardiac events dramatically in this population with low LDL cholesterol levels. Clinicians should keep in mind that these results may not be generalizable directly to women, people of color, or patients without coronary disease.

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## Are SSRIs and TCAs equally effective for the treatment of panic disorder?

Otto MW, Tuby KS, Gould RA, McLean RYS, Pollack MH. An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder. *Am J Psychiatry* 2001; 158:1989-92.

■ **BACKGROUND** Selective serotonin reuptake inhibitors (SSRIs) are commonly used as first-line treatment for panic disorder. However, comparative efficacy trials are lacking between older antidepressants, specifically the tricyclic antidepressants (TCAs), and SSRIs in the treatment of panic disorder. The authors use data gathered from efficacy trials to compare the efficacy, safety, and tolerability of SSRIs and TCAs used in the treatment of panic disorder.

■ **POPULATION STUDIED** This meta-analysis included double-blind, placebo-controlled efficacy trials of SSRIs for panic disorder in patients with or without agoraphobia. The trials that met these established criteria were published from 1990 to 1998 and included 1741 patients (mean sample size: 145 patients). A comparison between the study populations could not be made since the trials did not contain patient demographic information for the SSRI and non-SSRI groups. This analysis excluded uncontrolled trials, case reports, and long-term or follow-up trials.

■ **STUDY DESIGN AND VALIDITY** The authors used MEDLINE, PsychLIT, discussions with colleagues, and reference sections from related articles to identify double-blind, placebo-controlled efficacy trials of SSRIs for panic disorder. The authors conducted an effect-size analysis on the 12 trials identified. They compared these findings with the results of a recently published meta-analysis using non-SSRI treatments for panic disorder. In the fixed-dose trials, only the effective doses of SSRIs were used in the calculation of effect sizes.

A more extensive literature search for trials could have been completed using other databases, especially the Cochrane Registry of Controlled Trials. Whether the individual trials used concealed allocation assignment with respect to the treatment groups is not mentioned.

■ **OUTCOMES MEASURED** The main outcome is the effect sizes of the SSRI and TCA groups. The authors calculated the effect size by subtracting the mean score of the post treatment comparison group from that of the post treatment active treatment group and then

dividing by the standard deviation of the post treatment comparison group. Tolerability was assessed by using the dropout rates for each study group.

■ **RESULTS** The mean effect size for acute treatment outcome in the SSRI group compared with placebo was 0.55, a number not significantly different from that of the non-SSRI group (0.55) or, more specifically, the imipramine group (0.48). The older but smaller SSRI trials were associated with larger treatment effect sizes, whereas the larger, more recently published SSRI trials showed a smaller benefit. In addition, a funnel plot analysis showed that smaller studies with a lower effect size were missing (publication bias against "negative" studies). The difference in the dropout rates between groups treated with SSRIs (24.6%), which were weighted to give larger trials a greater contribution, was not significantly different from that of the other antidepressants (25.4%), specifically imipramine (22.4%). Using dropout rates as the only measure of tolerability may not be optimal. Not every patient who experienced adverse effects to the drug dropped out of the study. Patients may have also dropped out of the study for reasons other than poor tolerability to the drug.

### RECOMMENDATIONS FOR CLINICAL PRACTICE

This study fails to support the hypothesis that SSRIs are more efficacious and better tolerated when compared with older antidepressants in the treatment of panic disorder. These results also contradict the popular belief that SSRIs are generally more tolerable than TCAs. TCAs can provide patients with an effective, well-tolerated, less-costly treatment for panic disorder. A similar conclusion was reached in a comparison between TCAs and SSRIs in the treatment of depression.<sup>1</sup>

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### REFERENCE

1. Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared to tricyclic antidepressants. A meta-analysis. *BMJ* 1995; 310:1433-8.

## In children hospitalized for asthma exacerbations, does adding ipratropium bromide to albuterol and corticosteroids improve outcome?

Goggin N, Macarthur C, Parkin PC. Randomized trial of the addition of ipratropium bromide to albuterol and corticosteroid therapy in children hospitalized because of an acute asthma exacerbation. *Arch Pediatr Adolesc Med* 2001; 155:1329-34.

■ **BACKGROUND** Adding 2 to 3 doses of ipratropium bromide (Atrovent) to conventional therapy with inhaled  $\beta$ -agonists and systemic corticosteroids improves lung function and decreases hospital admissions when given in the emergency department (ED). This study evaluated whether ipratropium bromide administration improves outcomes in children who require subsequent hospitalization.

■ **POPULATION STUDIED** The authors enrolled 80 children aged 1 to 18 years with a history of asthma admitted to the pediatric inpatient unit of a tertiary-care urban hospital. Children had to have moderate to severe symptoms upon admission, defined as requiring inhaled  $\beta_2$ -agonists at least every 2 hours, having a forced expiratory volume in 1 second (FEV<sub>1</sub>) of 25% to 80% of predicted, or having a clinical asthma score of 3 to 9 out of a possible 10. The clinical asthma score is a total of 5 items—respiratory rate, wheezing, inspiratory–expiratory ratio, retracting, and observed dyspnea—scored on a 3-point scale. Excluded patients had coexisting cardiac, neurologic, immunosuppressive, or other chronic pulmonary disease, hypersensitivity to the study drugs, or known ocular abnormalities. Children were excluded if their asthma score was 10, if they needed airway intervention, or if more than 12 hours had elapsed between the first nebulizer treatment and admission.

■ **STUDY DESIGN AND VALIDITY** This was a double-blind randomized controlled trial. Study patients received frequent nebulized albuterol at 0.15 mg/kg as well as either IV hydrocortisone at 4 to 6 mg/kg every 6 hours or oral prednisone 1 mg/kg once daily. Attending physicians determined nebulizer treatment frequency, ranging from 30 minutes to 4 hours. Subjects were randomized to receive either ipratropium bromide or normal saline, matched to the albuterol dosing interval. Participants were stratified by age (less than 5 years vs 5 years or more) and by the number of ipratropium bromide doses they received in the ED (3 or less vs more than 3).

Investigators used an intention-to-treat analysis and allocation was concealed.

This study was well designed and well executed. The authors reported that the study had a 90% power to detect a difference in clinical asthma score as small as 0.9. The authors defined a “clinically meaningful difference” as a change in the clinical asthma score of 1.5.

■ **OUTCOMES MEASURED** The primary outcome was the clinical asthma score, measured at baseline and every 6 hours until discharge. The clinical score is reproducible, valid, and predictive. Secondary outcomes included oxygen saturation, FEV<sub>1</sub>, length of stay, time to a 4-hour albuterol dosing interval, and readmission to the hospital or ED within 72 hours of discharge.

■ **RESULTS** Of the 212 patients assessed for the trial, only 99 were eligible. Of these, 84 parents consented to enroll their children (4 children were later determined not to meet inclusion criteria and were excluded). The ipratropium and placebo groups were essentially the same. There was no difference in the asthma score between treatment and control groups in 3 of the 4 subgroups. In one subgroup—those who had fewer than 3 doses of ipratropium bromide in the ED—ipratropium provided a slight benefit. The difference in change in scores was 0.5 on the clinical asthma score, a statistically but not clinically important change. There were no differences in the secondary outcomes. The average heart rate was 6 to 10 beats per minute greater in the ipratropium group. The authors noted no transient anisocoria, a potential adverse effect of ipratropium bromide in children.

### RECOMMENDATIONS FOR CLINICAL PRACTICE

Giving ipratropium bromide to children with moderate to severe asthma exacerbations reduces admissions and asthma symptoms when given with appropriate  $\beta$ -agonists and corticosteroids in the ED. Ipratropium bromide provides no further benefit for children who require hospitalization after receiving the drug in the ED; therefore, adding ipratropium bromide to standard in-hospital care is not beneficial.

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## Which is more effective for as-needed treatment of seasonal allergy symptoms: intranasal corticosteroids or oral antihistamines?

Kaszuba SM, Baroody FM, de Tineo M, Haney L, Blair C, Naclerio RM. Superiority of an intranasal corticosteroid compared with an oral antihistamine in the as-needed treatment of seasonal allergic rhinitis. *Arch Intern Med* 2001; 161:2581-7.

■ **BACKGROUND** Symptoms resulting from early response to allergen exposure are histamine mediated, last a few minutes, and often cue patients to take medication. Hours later, the late response begins and typically leads to symptoms of congestion. The late-phase response is not histamine mediated; other studies have shown intranasal corticosteroids to inhibit the response. The researchers tested the hypothesis that intranasal steroids may be as beneficial as or superior to antihistamines for as-needed use because of their effect on the late response to environmental allergens.

■ **POPULATION STUDIED** The 88 subjects, aged 18 to 48 years, had fall seasonal rhinitis for at least 2 ragweed seasons before enrollment and had a positive puncture skin test to ragweed antigen extract. The population was 52% male, 60% white and in general good health. Patients were excluded for nasal polyps, displaced septum, perennial rhinitis, and signs or symptoms of renal, hepatic, or cardiovascular disease. Patients were also excluded if they had received immunotherapy within 2 years before enrollment or had taken topical or systemic steroids, antihistamines, decongestants, or cromolyn sodium within 2 weeks before enrollment.

■ **STUDY DESIGN AND VALIDITY** This is a randomized unblinded study. Patients were enrolled before or during the early part of the ragweed season. They were randomized to receive 100 µg/day fluticasone propionate per nostril or 10 mg loratadine once daily as needed for 4 weeks. Nasal lavage for eosinophil count and eosinophil cationic protein (ECP) and completion of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ, a validated instrument) were performed initially, at 2 weeks, and at 4 weeks. Patients were instructed to record medication usage and symptom severity in a diary twice daily. Itchy eyes and 3 symptoms for each nostril (rhinorrhea, nasal congestion, and sneezing) were rated on a scale of 0 to 3, ranging from 0 = no symptoms to 3 = severe symptoms.

Patients in the steroid group took the medications an average of 61% of the days of the study. This rate

probably approaches the compliance rate when intranasal steroids are prescribed for daily usage. Therefore, this trial may actually be measuring the effect of as-needed antihistamines compared with that of intranasal steroids prescribed daily.

The major limiting factor for this study was that patients were not blinded to treatment and, as a result, could have been influenced by their perceptions of benefit. It is likely that these patients were treated in the past with both types of products. Some may have had the impression that nasal steroids, which often are prescribed as second-line medications, are inherently more effective. The results may not be applicable to all antihistamines or to all intranasal steroids. Of particular concern is that loratadine is not especially effective when compared with other nonsedating antihistamines.

■ **OUTCOMES MEASURED** The RQLQ score was the primary outcome. The symptom diary scores were evaluated by symptom; a total symptom score was calculated. Other outcomes included nasal lavage eosinophil count and ECP levels.

■ **RESULTS** Patients used medication an average of 17 of 28 days in the fluticasone group, similar to the average of 18 of 28 days in the loratadine group. The RQLQ scores were similar in the 2 groups initially. Significant improvement in the fluticasone group over the loratadine group was seen at the second and third visits in the overall score and activity, sleep, practical, and nasal domains of the RQLQ ( $P < .05$ ). Symptom diaries showed a median score of 7.0 out of 21 for the loratadine-treated group and 4.0 out of 21 for the steroid-treated group ( $P = .005$ ). Eosinophil count and ECP showed significant decreases in the steroid group.

### RECOMMENDATIONS FOR CLINICAL PRACTICE

This study shows that for as-needed treatment of allergic rhinitis, fluticasone propionate appears to be superior to loratadine in both subjective and objective measurements. A double-blind design would have strengthened our confidence in these results. Regular use of intranasal steroids has also been demonstrated to provide better symptom control than antihistamines do. The clinician may consider prescribing as-needed antihistamines or intranasal steroids for first-line treatment of allergic rhinitis.

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## Are paroxetine, fluoxetine, and sertraline equally effective for depression?

Kroenke K, West SL, Swindle R, et al. Similar effectiveness of paroxetine, fluoxetine, and sertraline in primary care. *JAMA* 2001; 286:2947-55.

■ **BACKGROUND** Although selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants, data comparing the effectiveness of the members of this class of antidepressants are limited. This study compared the effectiveness of 3 SSRIs in a naturalistic study designed to mimic typical primary care prescribing.

■ **POPULATION STUDIED** Adult outpatients from 2 primary care research networks were eligible for the study if their primary care doctor had diagnosed a depressive disorder requiring medication. Patients were excluded if they were cognitively impaired, terminally ill, or suicidal; lived in a nursing home; were currently taking a non-SSRI antidepressant; or had recently taken an SSRI antidepressant. Data were analyzed from 546 patients (79% of those invited to participate), who were randomized and completed at least 1 follow-up interview.

■ **STUDY DESIGN AND VALIDITY** This was a randomized, controlled, unblinded trial designed to reflect actual primary care practice. After being diagnosed by their primary care physician (PCP) with clinical depression, with the PCP using his or her usual methods to make the diagnosis, patients were randomized through a concealed allocation procedure to receive daily doses of 20 mg paroxetine (Paxil), 20 mg fluoxetine (Prozac), or 50 mg sertraline (Zoloft). Both the patients and doctors were aware of the medication assignment. The PCP could adjust the dose to clinical response or change patients to a different medication. By the end of the study, less than half of the patients were taking the medication they had originally started.

The 3 groups were similar in baseline characteristics and in adherence to the study medications. Data analysis was by intention to treat. The outcomes assessors were not blind to treatment group assignment. Among this study's strengths are the large sample size and the naturalistic design that included physicians from a variety of community practices and patients with comorbid illnesses.

Three limitations are worth noting. First, adherence to the initially assigned medication was low; less than half of the patients were still taking their initially assigned medication on completing the study.

Second, the outcomes assessors were not blinded to the patients' medication assignments. Third, in contrast to usual clinical practice, the medications were provided free of charge to the study participants.

■ **OUTCOMES MEASURED** The primary outcome was change in the Mental Component Score (MCS) of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). The scoring of the MCS incorporates elements of the 8 subscales of the SF-36 and ranges from 0 to 100, with higher scores representing better mental health. Several other measures of depression and social functioning provided secondary outcomes.

■ **RESULTS** Forty-one percent to 50% of participants stopped their initially assigned medication during the 9-month follow-up period. About 20% of participants switched to another antidepressant. Roughly 25% stopped taking antidepressants altogether before completion of the follow-up period.

Starting with any of the 3 agents, however, resulted in good outcomes. For the entire sample, the mean MCS improved from 30.9 at baseline to 48.3 at 9 months. The proportion of the sample meeting criteria for major depression decreased from 74% at baseline to 26% at 9 months. MCS improved similarly in the 3 groups (an average of about 16 points, a statistically significant and clinically meaningful change). There were no significant differences in psychological outcome measures among the SSRI treatment groups.

### RECOMMENDATIONS FOR CLINICAL PRACTICE

This well-designed study of SSRI treatment for clinical depression in primary care settings found that paroxetine (Paxil), fluoxetine (Prozac), and sertraline (Zoloft) were equally effective for the treatment of depression. Additionally, since the rates of adherence and of adverse effects were similar among the 3 study medications, physicians should feel equally confident prescribing any of these SSRIs. Using the lowest-cost SSRI (fluoxetine just became available generically) is an ethical and reasonable approach.

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