Can high-dose supplementation with vitamins C and E, beta carotene, and zinc slow the progression of macular degeneration?


**BACKGROUND** Age-related macular degeneration (ARMD) is the leading cause of blindness in the United States among people aged 65 years or older. Observational and experimental data suggest that antioxidant or zinc supplements may delay progression of ARMD and visual loss.

**POPULATION STUDIED** Eleven retinal specialty clinics enrolled participants aged 55 to 80 years in 4 ARMD categories determined by the size and extent of drusen and retinal pigment epithelial abnormalities in each eye, the presence of advanced ARMD (each determined by evaluation of color photographs at a reading center), and visual acuity. Persons in category 1 had no ARMD; those in category 2 had mild or borderline ARMD; those in category 3 had moderate ARMD; and those in category 4 had advanced ARMD. At least 1 eye had a best corrected visual acuity of 20/32 or better (the study eye). Among participants, 56% were women, 96% were white, and the median age was 69 years. Potential participants were excluded for illness or disorders (history of cancer with a poor 7-year prognosis, major cardiovascular or cerebrovascular event within the previous year, or hemochromatosis) that would have made long-term follow-up or compliance with the study protocol unlikely or difficult.

**STUDY DESIGN AND VALIDITY** This was a randomized, double-masked, placebo-controlled trial (concealed allocation assignment). Participants were assigned to 1 of 4 treatment groups: (1) antioxidants (500 mg vitamin C, 400 IU vitamin E, 15 mg beta carotene); (2) 80 mg zinc as zinc oxide and copper, 2 mg as cupric oxide; (3) antioxidants plus zinc; or (4) placebo. The groups did not differ in their baseline characteristics. Average follow-up was 6.3 years, with 2.4% lost to follow-up. Analysis was by intention to treat. The judicial assessors of outcomes were masked to treatment group assignment.

**OUTCOMES MEASURED** Two primary outcomes were defined for study eyes in the ARMD trial: (1) progression to advanced ARMD and (2) at least a 15-letter decrease in visual acuity score.

**RESULTS** Patients with no ARMD (category 1) and mild or borderline ARMD (category 2) did not benefit from antioxidant and/or zinc supplementation. However, participants in the moderate and advanced ARMD groups (categories 3 and 4) had a lower risk of progression to advanced ARMD and visual acuity loss in the good eye if they took both zinc and antioxidants compared with placebo for 7 years (35.7% vs 26.7%, respectively; \( P < .001 \); number needed to treat = 11).

**RECOMMENDATIONS FOR CLINICAL PRACTICE**

Patients with moderate to advanced ARMD should consider taking an antioxidant/zinc supplement. Treatment of 11 such patients with high-dose supplementation of vitamin C, vitamin E, beta carotene, and zinc for 7 years will prevent progression of ARMD in one of them. Although some may argue that the results of this study justify routine screening for this condition, we need further evidence on both the number needed to screen for a benefit and the overall cost-to-benefit ratio of the intervention. In addition, we should remember that beta carotene has been linked to an increased risk of lung cancer in smokers.

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CONTINUED ON PAGE 109
Are progesterone or progestogens effective in managing premenstrual syndrome (PMS) symptoms?


- **BACKGROUND** Progestational therapy has been claimed effective in patients with PMS for many years. In the United States, progesterone or progestogen products account for 60% to 70% of prescriptions for PMS symptoms.

- **POPULATION STUDIED** The authors searched for clinical trials of progesterone or progestogens in the management of PMS. A systematic search of multiple databases in all languages yielded the reports of clinical trials included in this review. A search of references cited and contact with pharmaceutical companies completed the list of trials for evaluation. The report does not indicate whether searches were performed by more than one person. Trials were included if patients had a pretreatment diagnosis of PMS. Ten trials of progesterone therapy, evaluating 531 patients, remained for analysis. For progestogen therapy, analysis included 4 trials comprising a total of 378 patients. Although the authors do not describe the patients from the included trials in detail, they probably represent patients seen in family practice settings.

- **STUDY DESIGN AND VALIDITY** The authors of this meta-analysis evaluated all trials for quality using 2 separate rating scales. The quality of available studies was low. The authors independently extracted data in duplicate from the trials selected for analysis. The authors eliminated trials from consideration if patients did not have a pretreatment diagnosis of PMS. It is not clear whether some trials were eliminated because of poor quality. The pooled trials were statistically homogeneous, indicating that the studies were comparable enough to combine their data. The authors, who also looked for publication bias, considered each specific type of progestational agent separately to ensure the comparison of like treatments. The validity of the review is excellent, although the low quality of the studies available for evaluation reduces our confidence in the results.

- **OUTCOMES MEASURED** The authors defined their primary outcome as the reduction in overall symptoms of PMS. The authors summarized outcomes by intention to treat, where possible. They calculated a standardized mean difference in effect of treatment and converted this statistic to an odds ratio (OR).

- **RESULTS** Trials of progesterone suppositories or pessaries showed a marginal effect in favor of placebo (OR = 0.93; 95% CI, 0.91-0.95). Oral micronized progesterone had marginal benefit (OR = 1.30; 95% CI, 1.25-1.36). When all trials of progesterone were combined, there was a small, but clinically insignificant, effect (OR = 1.05; 95% CI, 1.03-1.08). Trials of progestogen therapy showed a clinically insignificant effect in favor of the drug (OR = 1.07; 95% CI, 1.03-1.11). Patients given active treatment had a nonsignificant increase in dropout rate because of side effects (OR = 1.65; 95% CI, 0.86-3.21).

**RECOMMENDATIONS FOR CLINICAL PRACTICE**

Progesterone and progestogen therapy should no longer be prescribed for PMS. This systematic review shows that published evidence does not support use of such therapy. Evidence of effectiveness in reducing overall symptoms of PMS is better for other therapies. Similar systematic reviews by the same group of authors show benefit from the use of selective serotonin-reuptake inhibitors (SSRIs) and vitamin B 6. For women with PMS symptoms that require pharmacologic management, SSRIs provide effective first-line therapy. Vitamin B 6 is also likely to be of benefit, although the quality of the evidence is poor. Nonmedication measures may help, but they have not been systematically studied. Calcium therapy and chasteberry fruit extract have been reviewed in previous POEMs and have been found effective.

**REFERENCES**


Can patients hospitalized with community-acquired pneumonia be treated safely and effectively with oral antibiotics?


**BACKGROUND** There is great variation in treatment strategies for community-acquired pneumonia. The authors of this study compared the safety, efficacy, and cost of oral therapy (in nonsevere pneumonia) and early switch to oral therapy (in severe pneumonia) with conventional parenteral treatment of community-acquired pneumonia in hospitalized patients.

**POPULATION STUDIED** The investigators enrolled 235 adults, 188 of whom were included in the final analysis. The patients had a diagnosis of pneumonia on the basis of clinical, laboratory, and radiologic criteria. Hospitalization was considered according to published standards: age >60 years, comorbid conditions, or severity criteria (PaO2<60mmHg, respiratory rate ≥30/min, heart rate at least 125/min, systolic blood pressure <90mmHg, temperature of ≥40˚C or <35˚C, altered mental status, multilobar involvement, or patients treated appropriately for 72 hours who showed deterioration or no improvement. Patients were excluded if they had been discharged from an acute-care facility in the previous 8 days or had nosocomial pneumonia, AIDS, aspiration pneumonia, extrapolmonary septic metastases, malabsorption, or problems swallowing. Patients were also excluded if they were pregnant or lactating or had criteria for admission to the intensive care unit. Patients were split into 2 study groups: those with nonsevere pneumonia who required hospitalization but did not meet any of these severity criteria, and those who had at least one severity criterion.

**STUDY DESIGN AND VALIDITY** This is a nonblinded, randomized controlled trial. The patients in both the nonsevere and the severe pneumonia groups were assigned to either a new therapeutic strategy or conventional treatment. Allocation was not concealed.

Patients with nonsevere pneumonia were treated either from the beginning with oral antibiotics (“new”) or initially with intravenous (IV) antibiotics and then switched to the oral route after 72 hours without fever (“conventional”). Oral antibiotics given were 500 mg cefuroxime axetil (Geftin) or 875/125 mg amoxicillin/clavulanate (Augmentin) 3 times a day. IV therapy consisted of 1 g cefonicid (Monocid) every 12 hours, 1500 mg cefuroxime (Zinacef) every 8 hours, or 1 g amoxicillin/clavulanate every 8 hours. In both groups a macrolide or quinolone was added if atypical microorganisms were suspected.

Patients with severe pneumonia were treated either initially with IV antibiotics and then switched to the oral route (200 mg cefpodoxime [Vantin] every 12 hours, plus clarithromycin or erythromycin) after 2 days (“new”) or treated with a full 10-day course of IV antibiotics (“conventional”).

This study was well done. The study groups did not differ in their baseline characteristics. Follow-up was complete and analyses were done on an intention-to-treat basis. Neither the patients nor the investigators were blinded to treatment groups and allocation of treatment groups was not concealed. A large number of patients were excluded from both the nonsevere group (21%) and severe pneumonia group (20%) for reasons of inappropriate enrollment. The greatest weakness of the study was the lack of statistical power to detect a difference between the groups. The authors were able to recruit only approximately half the desired number of study patients.

**OUTCOMES MEASURED** The main outcomes were treatment failure, including death, time to resolution of morbidity, and cost. Other outcomes were length of hospital stay, length of IV and total antibiotic therapy, time until resumption of normal activities, radiologic worsening at 48 hours, and adverse events.

**RESULTS** In patients with nonsevere pneumonia, no significant differences were found in mortality or time to resolution of morbidity, and cost. Other outcomes were length of hospital stay, length of IV and total antibiotic therapy, time until resumption of normal activities, radiologic worsening at 48 hours, and adverse events. Fewer adverse events occurred in the oral and early-switch groups, largely because of infusion-related phlebitis (NNT = 4). Significant cost savings occurred among patients with severe pneumonia in the early-switch group, primarily because of their shorter hospitalization.

**RECOMMENDATIONS FOR CLINICAL PRACTICE**

IV antibiotics need not be given for nonsevere pneumonia. In patients with severe pneumonia, starting treatment with IV antibiotics and switching to oral therapy after 2 days resulted in the same outcomes as did 10 days of IV antibiotics.

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CONTINUED ON PAGE 112
Does long-term erythromycin treatment reduce the number of common cold infections and subsequent exacerbations in patients with chronic obstructive pulmonary disease (COPD)?


**BACKGROUND** Simple viral respiratory infections (the common cold) often predispose patients with COPD to lower respiratory infections and subsequent exacerbations. Low-dose, long-term erythromycin therapy has been reported to treat diffuse panbronchiolitis and bronchiectasis by anti-inflammatory mechanisms rather than through its inherent antibacterial mechanisms. Macrolide antibiotics have also been reported to have antiviral protective mechanisms. This study investigated the frequency of common colds and COPD exacerbations in patients treated with low-dose, long-term erythromycin.

**POPULATION STUDIED** This Japanese study included 109 patients with COPD as defined by the American Thoracic Society. Subjects could be treated with sustained-release theophylline and inhaled anticholinergic agents, but not corticosteroids. The investigators excluded patients with diffuse panbronchiolitis or bronchiectasis.

**STUDY DESIGN AND VALIDITY** This was a randomized, nonblinded study conducted over 12 months. One group of 55 patients received erythromycin (200-400 mg daily); the control group of 54 patients received 10 mg riboflavin daily. The investigators were unaware which treatments would be given before enrolling patients into the study (ie, allocation was concealed). The groups were similar in age, sex, and baseline lung function. Patients self-reported daily symptoms, including sneezing, nasal discharge, malaise, headache, chills, fever, sore throat, hoarseness, and cough, and rated each for severity on a scale of 0 to 3. An episode of common cold was defined as a quantitative symptom score of >5. COPD exacerbations were defined as a worsening in symptoms requiring changes to the regular pharmacologic regimen, including the need for antimicrobial or systemic steroid therapy. Exacerbations were graded based on need for hospitalization: mild and moderate, if treatment did not require hospitalization; severe, if hospitalization was required. Physicians evaluated their patients every 2 weeks. Patients who had cold symptoms were encouraged to visit the hospital for investigator-initiated checks.

The combination of nonblinded subjects and the subjective nature of the measured outcomes limit the validity of the results of this study. These limitations are important because patients who knowingly receive antibiotics may tend to underestimate or underreport the severity or frequency of their cold symptoms. This bias would lead to an overestimation of the effectiveness of erythromycin.

**OUTCOMES MEASURED** The investigators measured the number of common colds and the frequency and severity of COPD exacerbations.

**RESULTS** The number of common colds was significantly lower in the erythromycin group than in the control group (1.24 vs 4.54 episodes per person; \( P = .002 \)). Over a 12-month period, 76% of the control group subjects experienced more than one cold, compared with 13% in the erythromycin group (relative risk = 9.26; 95% CI, 3.92-31.74; number needed to treat [NNT] = 1.6). The percentage of patients having one or more COPD exacerbations was significantly higher in the control group (54% vs 11%; RR = 4.71; 95% CI, 1.53-14.5; NNT = 2.2). The control group experienced 11 severe exacerbations; the erythromycin group had none. The total number and severity of COPD exacerbations were also significantly lower in the erythromycin group than in the control group. No deaths were reported during the study period. One patient in the erythromycin group was excluded because of adverse effects of treatment (diarrhea and anorexia).

**RECOMMENDATIONS FOR CLINICAL PRACTICE**

The frequency of common colds and of subsequent COPD exacerbations was significantly lowered in patients taking a low-dose of erythromycin daily for 1 year. This effect may be a result of the anti-inflammatory and antiviral mechanisms of macrolide antibiotics. Unfortunately, because neither the investigators nor the study subjects were blinded, the reported magnitude of this benefit may not be accurate. Additionally, these patients were not using corticosteroid therapy, which would have provided an anti-inflammatory benefit. The potential risk of emerging erythromycin/macrolide-resistant pathogens should restrict liberal prophylactic use. Considering the limitations of the study design and the risk of antibiotic resistance, we do not recommend prophylactic erythromycin treatment for common cold prevention in COPD patients.
Should patients with acute cough or bronchitis be treated with β2-agonists?


**BACKGROUND** Acute cough and bronchitis are common primary care diagnoses often treated with β2-agonists (eg, albuterol). This systematic review sought to assess whether β2-agonists constitute effective treatment for these conditions.

**POPULATION STUDIED** A total of 492 patients older than 2 years was gathered from randomized controlled trials measuring the efficacy of β2-agonists versus placebo or erythromycin for treatment of “acute cough,” “acute bronchitis,” or “acute transient cough” without clear etiology (pneumonia, pertussis, or sinusitis). The maximum mean duration of cough acceptable for inclusion was 30 days. Although no information was provided about specific diagnostic criteria, numbers of adult smokers and wheezers, or specifics of clinical presentation (fever, tachypnea), the population studied seems similar to that of a typical family practice.

**STUDY DESIGN AND VALIDITY** The authors searched multiple databases, including MEDLINE and EMBASE, The Cochrane Library, reference lists of retrieved articles, review articles, textbooks, and information from manufacturers. Two investigators examined the search results, forwarding those that met inclusion criteria to the remaining 3 investigators, who graded the studies using the Jadad methodology scale, on the basis of randomization, blinding, and withdrawals. Disagreement regarding study quality was common (κ = 0.27) and was resolved by discussion. Included studies were then divided into 3 groups for analysis: 2 pediatric trials comparing β2-agonists with placebo; 4 adult trials comparing β2-agonists with placebo; and 1 adult trial comparing β2-agonists with erythromycin. Summary statistics were generated using Review Manager 4.1.

Methodologic strength was adequate. The search for articles was thorough. The investigators grading the studies were blinded to the identifying information and results of the articles. Weaknesses include the small combined number of patients, which limited power, and the failure to address confounders in the adult studies, such as smoking, underlying noninfectious pulmonary disease, and co-interventions. Study weaknesses that handicapped the review include the lack of total time to improvement as a measured outcome; the short study durations (maximum 7 days); the predominant use of oral β2-agonists (5 of 7 studies), which are widely regarded as inferior to the inhaled type; and the lack of spacer use (suboptimal delivery).

**OUTCOMES MEASURED** Outcomes measured included cough severity, duration, and productivity; lost work days; night cough; and adverse effects. Only one trial measured compliance. Cost and patient satisfaction were not addressed.

**RESULTS** The overall quality of the included studies was fair. The pediatric studies revealed no benefit from albuterol. In the adult placebo trials, 1 demonstrated no benefit and 3 demonstrated slight improvement in cough severity. In the erythromycin study, those in the albuterol group had less cough or productive cough after 7 days, but the groups did not differ in night cough, time to improvement, or missed work days. When all the adult studies were combined, there was no difference in cough after 7 days, in productive cough, or in night cough. Studies that had enrolled more wheezing patients were more likely to show benefits than those that had not.

With regard to adverse effects, 11% of the pediatric albuterol group had shaking or tremor (relative risk [RR] = 6.76, number needed to treat [NNT] = 9); none of the placebo group experienced these effects. In the adult studies that recorded adverse effects, 35% to 67% of the albuterol groups and 0% to 23% of the placebo groups complained of tremor, shaking, or nervousness (RR = 7.94, NNT = 2.3).

**RECOMMENDATIONS FOR CLINICAL PRACTICE** This systematic review demonstrates that oral β2-agonists provide little benefit for patients with uncomplicated bronchitis and may have adverse effects. Clinicians should keep in mind that the total number of trials in this review is limited and that their quality is fair. Further research is needed to evaluate β2-agonist utility in patients who are also wheezing or smoking, to compare oral vs inhaled β2-agonists with properly used spacers, and to assess the potential contributions of other symptomatic therapies.
Does long-term bupropion (Zyban) use prevent smoking relapse after initial success at quitting smoking?


**BACKGROUND** Regardless of the intervention used, relapse after initial smoking cessation occurs in 70% to 80% of patients within 6 to 12 months. The investigators studied whether continuing bupropion treatment after initial success would decrease the relapse rate.

**POPULATION STUDIED** The investigators enrolled 784 men and women, aged 18 years or older, who had smoked 15 cigarettes or more per day for the previous year. Participants were motivated to stop smoking and were generally in good health. The investigators excluded persons dependent on alcohol or other non-nicotine substances in the previous year, those using psychotropic medications or with a history of bupropion use, those currently using tobacco products other than cigarettes, and those currently using another therapy for smoking cessation.

**STUDY DESIGN AND VALIDITY** This was a multicenter randomized double-blind placebo-controlled trial. All participants were given self-help material and took 300 mg bupropion sustained-release daily for 7 weeks. The subjects were instructed to set a target quit date 1 week after initiating treatment. Participants who had abstained from smoking cigarettes at week 7 were randomized to receive either bupropion or placebo for a total of 1 year. Allocation to treatment group was concealed and intention-to-treat analyses were performed. Participants returned for 14 visits during the first year (the medication phase) and for 5 visits during the follow-up year. All participants received the same educational material and counseling at each visit throughout the study.

The 40% long-term success rate after cessation is higher than that of previous studies. The 55% to 60% abstinence rate of those taking bupropion may pose an unrealistic expectation for care providers. These results were obtained in a select group of smokers who were highly motivated, who were intensely monitored (20 clinic visits over 2 years), and who received behavioral counseling at every visit.

**OUTCOMES MEASURED** The study had 3 primary outcomes: (1) abstinence the week preceding each visit during the first year; (2) continuous abstinence during medication treatment; and (3) time to first relapse. Smoking status was defined by self-report of abstinence over the previous 7 days, confirmed with an expired air / carbon monoxide measurement at each visit. Relapse was defined by self-report, by expired air / carbon monoxide levels, or by missing 2 or more consecutive visits. Participants who were abstinent at every visit were classified as continuously abstinent.

**RESULTS** Of the 784 participants enrolled in the open-label bupropion phase of the study, 461 (58.8%) were abstinent at week 7. Of these, 429 were randomized to receive placebo or bupropion for 45 weeks. A total of 347 (80.9%) remained in the study through the first year. Most participants (317, 75.9%) completed the entire 2 years of the study. Dropout rates were similar in the treated and untreated groups. At the end of 1 year, 55.1% of the treated patients were not smoking, compared with 42.3% in the placebo group ($P = .001$, NNT=8). At 18 months, significantly more treated patients were still not smoking (47.7% vs 37.7%, number needed to treat = 10). At the end of 2 years, however, abstinence rates were similar for the 2 groups (41.6% vs 40%). The drug was well tolerated. Insomnia and headache were the most common adverse effects.

**RECOMMENDATIONS FOR CLINICAL PRACTICE**

Highly motivated patients who stop smoking during the standard 7-week bupropion program are likely to maintain abstinence as long as they continue to take the drug, at least for 1 year. Once they have discontinued the drug, however, the relapse rate in this group is the same as for those in the standard program. It is reasonable to offer bupropion indefinitely to certain patients who are able to quit smoking after the standard program—those who can afford it or perhaps those for whom another indication to take bupropion is identified—as long as the clinician informs them of the available data on relapse after they have ended their participation in the program.

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CONTINUED ON PAGE 175
Can a simple warfarin initiation scheme predict the maintenance dose in patients with nonrheumatic atrial fibrillation?


**BACKGROUND** Initiating warfarin in patients with atrial fibrillation at a typical loading dose of 10 mg daily for 2 days may be associated with excess anticoagulation, especially in older patients. In addition, daily monitoring associated with this regimen may be inconvenient for outpatients. Initiating warfarin at 5 mg daily may produce more consistent anticoagulation and eliminate the need for daily monitoring. The investigators tested whether administering 5 mg warfarin daily for 4 days and checking the anticoagulation status via the international normalized ratio (INR) on the fifth day could predict an early warfarin maintenance dose.

**POPULATION STUDIED** This study included 61 outpatients with nonrheumatic atrial fibrillation, not receiving heparin, between the ages of 42 to 88 years (mean age = 71 years). Patients were excluded from the study if they were being treated with a drug known to interact with warfarin or had a coagulation disorder, contraindication to warfarin therapy, previous course of anticoagulation treatment, or baseline INR > 1.2, or if they refused to participate.

**STUDY DESIGN AND VALIDITY** This was a prospective cohort study in which patients were given 5 mg warfarin daily for 4 days (day 1 to day 4). The INR was measured on day 5 and the patient’s physician freely chose a new dose. The INR was checked at least once a week for the next 2 weeks. Patients were followed for 3 months. The warfarin dose was considered stable when the INR was between 2 and 3 on 3 consecutive occasions at least 1 week apart. The stable weekly warfarin dose was plotted against the INR obtained on the fifth day of initiation to establish a scheme for predicting an early warfarin maintenance dose. To test the validity of this scheme, 23 additional patients with nonrheumatic atrial fibrillation were given the predicted warfarin maintenance dose based on their INR on day 5 and were followed for 3 months. Although only 23 patients were tested using this warfarin dosage scheme, clinicians may consult it when choosing a warfarin maintenance dose rather than using the trial-and-error method that is often pursued in daily practice.

**OUTCOMES MEASURED** The outcome of this study was to determine whether the INR on day 5 of warfarin treatment could predict an early warfarin maintenance dose. Major and minor bleeding episodes and thromboembolic complications were also measured.

**RESULTS** Of 91 patients eligible to participate in the study, 61 were included in the analysis. Thirty patients could not be evaluated either because they failed to reach a therapeutic INR within 3 months or because they did not complete the follow-up period. During the evaluation phase that was conducted in 23 additional patients, the mean difference between the predicted and actual doses of warfarin was 1.6 mg/week (95% CI, 0.007-3.195 mg) with a maximum difference of 9 mg/week. One minor bleeding episode was reported among the 61 initial patients and 23 additional patients. The dosing regimen, based on the INR after 4 days of 5 mg warfarin, is shown in the Table.

### TABLE

<table>
<thead>
<tr>
<th>INR on Day 5</th>
<th>Approximate Daily Warfarin Dose (mg)*</th>
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<td>1.8</td>
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*Doses are rounded and calculated from a cumulative weekly dose.

**RECOMMENDATIONS FOR CLINICAL PRACTICE**

Starting outpatients with 5 mg per day of warfarin and basing a maintenance dose on the INR obtained on the fifth day is an effective way to initiate therapy. The difference between the actual and predicted maintenance doses was small, indicating that this simple scheme is a good model for predicting the warfarin maintenance dose. Although only 23 patients were tested using this warfarin dosage scheme, clinicians may consult it when choosing a warfarin maintenance dose rather than using the trial-and-error method that is often pursued in daily practice.

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Which oral triptans are effective for the treatment of acute migraine?


**BACKGROUND** Six selective serotonin 5-HT1B/1D agonists (triptans) are currently approved and available in the United States; 1 more may eventually be approved. Although clinicians need evidence of the differences in efficacy and safety of these agents to assist in their prescribing decisions, a lack of head-to-head comparison trials makes this assessment difficult. The authors performed a meta-analysis of multiple trials of oral triptans to determine their relative effectiveness in treating acute migraine.

**Population Studied** Patients eligible for the studies were aged 18 to 65 years, had moderate to severe migraine, and had pain rated on a 4-point scale (0 = no pain; 3 = most severe pain). A total of 24,000 patients from 53 clinical trials met the criteria. The authors selected 100 mg sumatriptan, the most widely prescribed agent, as the reference dose.

**Study Design and Validity** The authors performed a systematic review of published English-language trials and asked the 6 pharmaceutical companies for raw data from published and unpublished trials. Five companies provided data on 6 drugs; the makers of frovatriptan did not. The investigators included studies that (1) were randomized double-blind controlled clinical trials (placebo or active comparison); (2) treated moderate or severe migraine attacks (by International Headache Society criteria) within 8 hours of migraine onset; (3) used an oral triptan at a recommended clinical dose; and (4) evaluated the headache on the 4-point pain scale. The authors excluded 23 studies that lacked a control group, used nonrecommended dosages, or studied special populations. Of the 53 trials reviewed, 31 were placebo-controlled trials and 22 were direct-comparison trials.

Since the inclusion criteria and outcome data collected were similar among the placebo-controlled studies, the authors combined the results to assess the evidence of the relative benefits of the different triptans. Results were reported as absolute gain and therapeutic gain (placebo response subtracted from the absolute gain). Adverse reactions were reported as therapeutic harm (differences between placebo and active drug reactions). Reporting results as therapeutic gain reduces the potential effect of varying placebo response rates among multiple trials. The comparison trials were analyzed separately.

The study is a strong meta-analysis. The authors used raw data from both published and unpublished randomized, double-blind trials. The studies had consistent classification of migraine pain and consistent use of defined outcomes. The report did not outline the methods used to search for clinical trials. In addition, the authors had to rely on self-reporting from the pharmaceutical companies for their data. The review did not report the severity of adverse drug reactions or the number of patients whose therapy was discontinued because of side effects.

**Outcomes Measured** Four outcomes were measured: (1) proportion of patients with a headache response (improvement to mild or no pain 2 hours post dose); (2) sustained pain-free response (2 hours post dose and no recurrence of moderate or severe migraine 2 to 24 hours post dose); (3) consistent effect of a medication over recurrent attacks in the same person; and (4) adverse reactions.

**Results** In placebo trials, 100 mg sumatriptan showed a mean absolute and therapeutic gain of 59% and 29% for 2-hour headache response and 29% and 10% for sustained pain-free rate. The mean therapeutic harm rate was 13% for at least 1 adverse event, 6% for 1 central nervous system event, and 2% for 1 chest event. On average, patients obtained relief for 2 of 3 consecutive migraines. Only 80 mg eletriptan had a statistically significant advantage over 100 mg sumatriptan for therapeutic gain in 2-hour headache response (number needed to treat [NNT] = 8). For therapeutic gain in 2-hour pain-free response, both 10 mg rizatriptan (NNT = 8) and 80 mg eletriptan (NNT = 13) had a statistically significant advantage. Adverse reaction rates were similar for most triptans but lower for 2.5 mg naratriptan and 12.5 mg almotriptan.

**Recommendations for Clinical Practice** This meta-analysis demonstrates that oral triptans are effective in relieving acute migraine headache with acceptable adverse effect rates and non-clinically relevant degrees of relief among the agents. The meta-analysis showed that only approximately 60% of patients respond to a specific triptan. In the few consistency trials, the triptans were effective in treating an average of 2 of 3 consecutive acute migraines in the same patient. Research supports nonsteroidal anti-inflammatory drugs as first-line therapy for mild to moderate migraine; triptans should be considered first-line therapy for moderate to severe migraine. We suggest that clinicians become familiar with several triptans and recognize that a given agent will not always relieve the same person’s migraine and that the failure of 1 triptan to help a patient does not predict failure with another triptan.

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