

The following abstracts, from medical journals containing literature on migraine management, were selected for their relevance to this Special Report supplement.

Two Sumatriptan Studies

Two double-blind multicenter trials were performed to evaluate an intranasal selective 5-hydroxytryptamine-1 (5-HT₁) receptor agonist, sumatriptan, in the acute treatment of migraine. Adults were randomized to self-administer sumatriptan nasal spray 20 mg (n=417), 10 mg (n=211), or placebo (n=213) during an acute migraine attack. Patient diaries showed that baseline pain became mild or nonexistent after 2 hours in 29% and 35% of placebo-treated patients in the 2 studies, versus 62% and 63% of patients treated with sumatriptan 20 mg ($P < 0.05$ in both studies) and versus 43% and 54% of patients taking the 10-mg dose ($P < 0.05$ in 1 study only). Onset of symptom relief was reported as early as 15 minutes postdose with the 20-mg dose in 1 study. About two thirds of patients treated with the 20-mg dose of this 5-HT₁ agonist got relief within 2 hours. At 2 hours postdose, clinical disability scores were reported as mild or normal in 47% and 58% of placebo-treated patients versus 72% and 74% of patients taking the 20-mg sumatriptan dose and 56% and 68% of patients taking the 10-mg dose. Relief of specific migraine symptoms including nausea, photophobia, and phonophobia was similarly dose related. The only treatment-related adverse events involved patients in all sumatriptan groups reporting bad, bitter, or unpleasant tastes more frequently (19% to 36%) than patients in the placebo groups (0% to 2%). Overall, the results of these US trials demonstrated that sumatriptan was effective and well tolerated for relief of acute migraine attacks. The authors concluded that sumatriptan offers an option for patients who dislike injectable medications or whose migraine-related gastrointestinal symptoms preclude use of oral medications.

Ryan R, Elkind A, Baker CC, Mullican W, DeBussey S, Asgharnejad M. Sumatriptan nasal spray for the acute treatment of migraine: Results of two clinical studies. *Neurology* 1997;49:1225-1230.

Finding the Best Zolmitriptan Dose

Zolmitriptan is a 5-hydroxytryptamine (5-HT_{1B/1D}) receptor agonist with good oral absorption characteristics and pharmacologic evidence of both central and peripheral actions. Approximately 1000 patients were randomized to receive placebo or oral zolmitriptan at 1 mg, 2.5 mg, 5 mg, or 10 mg for a severe or moderate migraine attack. Overall, efficacy results with zolmitriptan doses at or above 2.5 mg were superior to placebo, with little additional symptom relief found in doses above this level. Improvements to levels of mild or no pain at 4 hours were reported by 57% of patients taking zolmitriptan 1 mg (n=125), 75% of those taking 2.5 mg (n=260), 77% of those taking 5 mg (n=245), and 78% of those taking 10 mg (n=248) versus just 32% of those taking placebo (n=121) ($P < 0.001$ for all doses versus placebo). Zolmitriptan at 2.5 mg also relieved nonheadache symptoms (eg, nausea, photophobia, and phonophobia) while lowering rates of activity impairment, headache recurrence, headache persistence, and rescue medication use. Tolerability of zolmitriptan was dose related, with a lower incidence of dizziness, paresthesia, and anesthesia reported in the 1-mg and 2.5-mg groups. Chest and throat tightness were also more frequently noted with the 5-mg and 10-mg dose of the 5-HT_{1B/1D} receptor agonist. Most reported adverse events were mild or moderate and brief in duration. However, severe adverse events after the first dose were reported in 2% of the placebo group and 6%, 3%, 12%, and 14% of the 1-mg, 2.5-mg, 5-mg, and 10-mg zolmitriptan groups, respectively. No serious adverse events were reported. Efficacy and tolerability results in this dose-ranging study indicated that 2.5 mg was the optimal initial dose for acute treatment of migraine pain.

Rapoport AM, Ramadan NM, Adelman JU, et al. Optimizing the dose of zolmitriptan (Zomig, 311C90) for the acute treatment of migraine: A multicenter, double-blind, placebo-controlled dose range-finding study. *Neurology* 1997;49:1210-1218.

Crossover Trial With 3 Naratriptan Doses

The selective 5-hydroxytryptamine-1 (5-HT₁) receptor agonist naratriptan interacts more potently *in vivo* and *in vitro* with craniovascular 5-HT₁ receptors than sumatriptan. It also has greater oral bioavailability and a longer half-life. In this double-blind crossover trial, all migraine patients received 4 different oral treatments, each to be self-administered at the onset of 4 separate moderate-to-severe migraine episodes. Efficacy and tolerability were evaluated for naratriptan 2.5 mg (586 patients), 1 mg (595 patients), 0.25 mg (591 patients), and placebo (602 patients). In all efficacy measures, a dose-related treatment effect was noted. Headache relief after 4 hours, for example, was observed in 68%, 57%, 39%, and 33% of groups taking naratriptan 2.5 mg, 1 mg, 0.25 mg, and placebo, respectively ($P < 0.001$ 2.5 mg and 1 mg versus placebo). This dose-related laddering pattern of relief persisted at 8, 12, and 24 hours postdose, with those patients using the 2 higher naratriptan doses requiring significantly less ($P < 0.001$) rescue medication or second doses compared to placebo. In terms of reducing the incidence of specific symptoms such as nausea and photophobia, the 2 higher doses of naratriptan also proved more effective ($P < 0.005$) than placebo. Similar results were seen in clinical disability reduction and headache recurrence, with the 2.5-mg naratriptan dose providing superior results. Patients taking naratriptan for acute migraine reported adverse events no more frequently than those taking placebo for such attacks. The authors conclude that naratriptan is effective and well tolerated in acute treatment of migraine.

Mathew NT, Asgharnejad M, Peykamian M, Laurenza A. Naratriptan is effective and well tolerated in the acute treatment of migraine: Results of a double-blind, placebo-controlled, crossover study. *Neurology* 1997;49:1485-1490.

Impact of Oral Sumatriptan

Although oral sumatriptan has previously been shown to be effective and well tolerated in the acute treatment of migraine, the effects of this drug on workplace productivity, ability to perform non-workplace activities, health-related quality of life, healthcare use, patient satisfaction with medication, and clinical effectiveness have not been assessed concurrently within the context of 1 clinical trial. This study, conducted in 220 nurses with migraine, examined the effect of oral sumatriptan on these variables for 6 months after usual therapy had been used for 2 months. On average, total disability time (ie, lost workplace productivity + lost activity time) because of migraine was 31% lower with sumatriptan than with usual therapy ($P < 0.001$). Patient scores on all dimensions of the Migraine-Specific Quality of Life Questionnaire and scores on 7 of 8 dimensions of the Short Form-36 Health Survey® improved after 6 months of sumatriptan treatment. The average number of migraine-related visits to a clinic or physician's office for migraine consultation was significantly lower ($P < 0.001$) during the sumatriptan phase compared with the usual therapy phase. Mean patient satisfaction scores were significantly higher ($P < 0.05$) for sumatriptan compared with usual therapy after both 3 months and 6 months of treatment. Headache relief 2 hours postdose was reported by 76% of patients across migraine days during the sumatriptan phase compared with 44% of patients during the usual therapy phase ($P < 0.001$). Data from this study demonstrate that oral sumatriptan may reduce both the economic and social costs of migraine for patients and their employers.

Adelman JU, Sharfman M, Johnson R, et al. Impact of oral sumatriptan on workplace productivity, health-related quality of life, healthcare use, and patient satisfaction with medication in nurses with migraine. *Am J Man Care* 1996;2:1407-1416.

Zolmitriptan 2.5 mg for Migraine Attacks

In this double-blind multicenter trial, patients averaging 1 to 6 migraine headaches per month were randomized to receive either zolmitriptan 2.5 mg ($n=219$) or placebo ($n=108$). Patients self-medicated for a single moderate or severe headache and recorded efficacy and adverse events in a diary. Levels of mild or no pain were reported by 26%, 36%, and 37% of placebo-treated patients at 1, 2, and 4 hours, respectively, versus 33%, 62% ($P < 0.001$), and 70% ($P < 0.001$) of zolmitriptan-treated patients at the same times. 4 hours after treatment, 38% of patients taking zolmitriptan were pain-free versus 13% of those taking placebo ($P < 0.001$). Patients treated with zolmitriptan also reported more favorable efficacy than placebo in terms of headache recurrence rates (22% recurrence for active treatment versus 30% for placebo) and response rates for nonheadache symptoms (eg, at 4 hours, 64% photophobia frequency for placebo versus 35% for zolmitriptan, and 44% nausea frequency for placebo versus 21% for zolmitriptan). Zolmitriptan was effective in subsets of patients with migraine upon awakening and migraine associated with menses. Overall incidence of patients reporting at least 1 adverse event was 46% for zolmitriptan and 29% for placebo. A higher percentage of the placebo group (12%) reported severe adverse reactions than did the zolmitriptan group (5%). No clinically serious adverse events were judged to be related to zolmitriptan. According to authors, these results confirm previous dose-finding studies showing zolmitriptan 2.5 mg to be clinically effective and well tolerated for the acute treatment of migraine.

Solomon GD, Cady RK, Klapper JA, et al. Clinical efficacy and tolerability of 2.5 mg zolmitriptan for the acute treatment of migraine. *Neurology* 1997;49:1219-1225.

Migraine Protocol Reduces Costs

Health costs of migraine due to clinic visits, hospitalization, lost productivity, and prescription drug use are substantial. This retrospective study estimated migraine-related costs before and after implementation of a drug-based migraine management protocol at a Department of Veteran Affairs Medical Center. Under the approved protocol for acute treatment, treatment choices progressed from prochlorperazine through dihydroergotamine, ketorolac, sumatriptan, and then narcotics. Neurology consults were available for patients not responding to these options. Preventive therapies such as propranolol, amitriptyline, methysergide, and verapamil were encouraged. Thirty-eight patients (20 male, 18 female) with a history of migraine (average 1.7 years since initial diagnosis) were identified. Chart and computer-based data on migraine-related resource use was collected for the 6-month periods before and after protocol implementation. Dollar values were assigned to costs such as emergency room (ER) visits, neurology clinic visits, and inpatient days. The average cost of migraine management over the 6-month period prior to protocol implementation was \$2468 per patient compared to \$727 per patient in the 6-month period immediately after protocol implementation, a significant reduction ($P = 0.0001$). All categories of mean per-patient resource consumption were reduced during the protocol phase: for example, average ER visit costs went from \$1051 to \$33, inpatient days from \$510 to \$224, and neurology clinic visits from \$423 to \$152 (all $P < 0.05$). Average prescription medication costs dropped from \$310 to \$257, but this change was not statistically significant. The researchers concluded that a health system protocol for prophylactic and abortive pharmaceutical management of migraine patients may reduce nonpharmaceutical and overall healthcare resource use. However, since the study was small and based on a nontypical migraine population (ie, more predominantly male, with more severe headaches, and fewer financial disincentives to seek care), they cautioned that further economic analysis in managed care settings is required.

Harrison DL, Coons SJ, Jones WN, Labadie EL. The economic impact of a protocol for the management of migraine headaches. *J Res Pharma Econ* 1996;7:35-48.

Migraine Prevalence in the United States

To improve baseline statistics about the scope of migraine in the United States, a survey with questions about severe headache was mailed to 15,000 households preselected to represent a cross-section of the US in terms of age, gender, household size, and geographic area. Responses from 20,468 household members between 12 and 80 years of age (62.4% of the surveyed population) were analyzed. Whites and the elderly were more likely to respond. Prevalence for all types of severe headaches was 27.3% for females and 13.9% for males. Based on symptoms defined by the International Headache Society, 17.6% of females and 5.7% of males had at least 1 migraine headache each year. Migraine prevalence was highest between the ages of 35 and 45 years, with the peak occurring slightly earlier in males. Prevalence was strongly associated with household income. Individuals from households with incomes below \$10,000 per year, for example, had a migraine prevalence that was 60% higher than those from households with income \$30,000 and over. A peak migraine prevalence of 40% was observed in women at approximately age 40 in the lowest income group; this compared with a prevalence of 22% in women of the same age in the highest income group. The female-to-male gender ratio for migraine prevalence varied from 2.0 to 3.3 depending on age. Rates of severe migraine-related disability were not related to gender, age, income, urban versus rural residence, or geographic location. Projecting survey results to the US population (1989 census), the authors estimated that 8.7 million females and 2.6 million males experienced migraine headaches with moderate-to-severe disability, with more than a third of these individuals suffering from at least 1 attack per month. The authors recommend that physicians become aware of the risk factors and sociodemographic influences associated with disabling migraines.

Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States: Relation to age, income, race, and other sociodemographic factors. *JAMA* 1992;267:64-69.

Intranasal Dihydroergotamine

The parenteral forms of dihydroergotamine mesylate (DHE) have been used extensively for emergency-room treatment of acute migraine attacks but remain poor choices for self-administration due to patient discomfort and inconvenience. To test the safety and efficacy of a more acceptable intranasal spray formulation, 310 migraine outpatients were randomized to self-administration of 2 mg DHE, 3 mg DHE, or placebo for 2 moderate or severe migraine headaches. The double-blind study recruited patients from 25 institutions. Overall, both nasal DHE doses led to significant increases in pain relief and functional ability, with significant decreases in pain intensity and nausea compared with placebo. 4 hours after treatment for their first headache, 70% of patients in the 2 mg group had no pain or mild pain compared with 28% in the placebo group ($P < 0.001$); for their second headache, the percentages were 68% and 36% ($P < 0.001$), respectively. Pain relief in patients taking 2 mg DHE was significantly superior ($P < 0.01$) to that reported in patients taking placebo as early as 30 minutes postdose; in patients taking the 3-mg dose, pain relief began 1 hour after dosing. In terms of improved functional ability, patients taking 2 mg DHE showed significant improvement over the placebo group at every time point beginning at 1 hour postdose; at 4 hours after treatment, 56% of patients taking DHE said they could function normally compared to 17% of those taking placebo. DHE-related decreases in photophobia, phonophobia, nausea, and use of rescue medication were also seen. No serious DHE-related adverse events were reported; minor adverse events involved route of administration (eg, rhinitis, taste perversion). In all measures, the 2-mg dose of DHE provided slightly superior pain relief and was associated with fewer side effects than the 3-mg dose; the authors cite previous studies where this "less is more" DHE phenomenon has been noted.

Gallagher RM. Acute treatment of migraine with dihydroergotamine nasal spray. *Arch Neurol* 1996;53:1285-1291.

Poor Ratings for Prophylaxis Studies

The authors rated the scientific rigor of published randomized, double-blind, placebo-controlled trials of migraine prophylaxis drugs. They also estimated US physician utilization of migraine prophylactic agents, assessed costs of these therapies, and then evaluated correlations between documented efficacy, utilization, and costs. Trials were rated on a 1 (low) to 5 (good) scale according to criteria such as adherence to International Headache Society standards, methodology description and statistical evaluation, drop-out rates, and sample size. Thus, each study had a quality-rating score for scientific rigor attached to its reported efficacy versus placebo. Overall, most studies of widely used anti-migraine agents lacked scientific rigor. In 18 trials of propranolol, where the reduction in headache frequency ranged from 10% to 76% (mean 33%), the average scientific score was only 1.44. In 4 verapamil studies, the mean frequency reduction was 28% and the rigor score was 1.00. And in 3 amitriptyline studies, the mean frequency reduction was 42% and the rigor score was 2.33. According to the authors, only flurbiprofen, tolfenamic acid, indobufen, metoprolol, divalproex, and fenoprofen achieved rigor scores high enough (3-5) to warrant confidence in their reported efficacy measures. A survey of 100 neurologists and 96 primary care physicians (PCPs) revealed that the top drug choices for migraine prophylaxis were propranolol (25% of neurologists and 28% of PCPs), verapamil (14% and 15%), and amitriptyline (15% and 12%). Approximately 10% of neurologists considered divalproex (rigor score = 3.75, 39% to 43% reduction in headache frequency in 4 studies) to be first- or second-line treatment while about 13% of PCPs preferred selective serotonin reuptake inhibitors. Statistical analysis showed that physician preference correlated with scientific merit of drug studies ($r = 0.644$, $P = 0.018$) but not drug cost. The authors conclude that the 3 most commonly selected migraine prophylactic agents have not been shown with complete scientific rigor to prevent migraine. Any benefits with these lower-cost drugs (eg, \$12.47/month for propranolol and \$4.35/month for amitriptyline) are marginal, certainly not exceeding placebo benefits by more than 50%. On the other hand, drugs with the most scientifically rigorous studies tend to have even lower efficacy rates and higher costs (eg, \$43.20/month for fenoprofen to \$67.20/month for flurbiprofen).

Ramadan NM, Schultz LL, Gilkey SJ. Migraine prophylactic drugs: Proof of efficacy, utilization and cost. *Cephalgia* 1997;17:73-80.

Naratriptan in 613 Migraineurs

This double-blind placebo-controlled evaluation of 3 different oral naratriptan doses involved 613 migraineurs at 54 US centers. Mean patient age was 40.2 years. Ninety-three percent were white, and 87% were women. Efficacy results were based on patient-rated scores at time of dosing and at predetermined intervals postdosing. At 4 hours postdose, headache pain was reduced from moderate/severe to mild/none in 60% of patients receiving naratriptan 2.5 mg (n=127) and in 50%, 35%, 32%, and 34% of those receiving naratriptan 1 mg (n=117), 0.25 mg (n=119), 0.1 mg (n=128), and placebo (n=122), respectively ($P < 0.05$ for 2.5 mg and 1.0 mg versus placebo). Similarly, clinical disability at this time was reported as mild/none for 70% of patients receiving naratriptan versus 63%, 47%, 48%, and 48% of those receiving naratriptan 1 mg, 0.25 mg, 0.1 mg, and placebo, respectively ($P < 0.05$ for 2.5 mg and 1.0 mg versus placebo). Meaningful relief was reported in 59% of patients taking the highest naratriptan dose versus 36% of patients taking placebo ($P < 0.001$). In all efficacy measures, including maintenance of headache relief and prevention of recurrence, the 2.5-mg dose was statistically better than placebo and the 2 lowest doses or naratriptan. Naratriptan was well tolerated, with the incidence of adverse events (including throat/chest tightness) not differing between active treatment and placebo groups. No dose-related increases in adverse events were noted. The researchers concluded that naratriptan 2.5-mg tablets offer the optimum benefit-to-risk ratio for this oral selective 5-hydroxytryptamine-1 receptor agonist.

Klassen A, Elkind A, Asgharnejad M, Webster C, Laurenza A. Naratriptan is effective and well tolerated in the acute treatment of migraine. Results of a double-blind, placebo-controlled, parallel group study. *Headache* 1997;37:640-645.

Dose-Ranging Sumatriptan Studies

Two European multicenter trials were designed to find the optimum dose of intranasal sumatriptan for acute treatment of migraine. Both studies compared efficacy and tolerability of placebo against sumatriptan at doses of 1 mg, 5 mg, 10 mg, 20 mg, and 40 mg. In 1 study (n=245), medication was administered as a single dose through 1 nostril; in the other study (n=210), the same doses were divided and administered through 2 nostrils. Patients reported to their clinic at first signs of migraine, submitted to baseline testing, received the randomized treatment, and then recorded their headache severity and symptoms for 3 hours. In both studies, the 5-hydroxytryptamine-1 (5-HT₁) receptor agonist at the 10-mg, 20-mg, and 40-mg levels was superior to placebo in headache improvement efficacy at 120 minutes ($P < 0.05$); in the single-nostril study, the 5-mg sumatriptan dose also outperformed placebo. In addition, the incidence of nausea, vomiting, photophobia, or phonophobia and the level of reported clinical disability were generally lower in patients receiving 5 mg or more of sumatriptan. Plasma sumatriptan levels increased in proportion to dose in both studies but no correlation was found between headache severity and pharmacokinetic parameters. The most frequently reported adverse event was dose-related taste disturbance, with incidence ranging from 3% to 26% of patient groups taking 1 mg to 40 mg sumatriptan (compared to rates of 0% to 8% in placebo groups). Based on the similarity of findings in the 2 studies, researchers concluded that administering sumatriptan as a divided dose through 2 nostrils did not improve efficacy compared to single-nostril administration. They said the 20-mg dose of sumatriptan provided the best efficacy, but further dosing studies were needed.

Salonen R, Ashford E, Dahlof C, et al. Intranasal sumatriptan for the acute treatment of migraine. *J Neurol* 1994;241:463-469.